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RELATIONSHIP BETWEEN CYSTIC DISEASE OF THE BREAST AND CARCINOMA

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MINNEAPOLIS

INTRODUCTION

Fifty years have passed since Reclus published his classic description of cystic disease of the breast. Since that time much investigative work has been done, and a voluminous literature has developed. However, the practical and important relationship between this disease and carcinoma has never been so decisively established that any one view has been generally accepted. As a result, a wide range of opinion still prevails as to what constitutes its proper treatment. Thus the selection of the surgeon, rather than the nature of the lesion, often determines whether a breast is removed or preserved.

I believe that sufficient evidence is available to justify a more uniform view of this relationship and to evolve a more standardized and conservative policy in the treatment of the disease.

It is proposed to review the literature, to evaluate the information contained in it, to add, together with follow-up information, a series of 290 cases of cystic disease of the breast in which operation was performed, and to draw certain conclusions which will be embodied in the form of recommendations as to the proper management of the disease.

DEFINITION OF TERMS

The many writers who have attempted to embody their various ideas of etiology in the names which they have applied to the disease have cluttered the literature with numerous terms serving no useful purpose and confusing to a reviewer of the subject.

To avoid this confusion, the term "cystic disease" is here used to cover the whole clinical and histologic picture of benign epithelial and connective tissue hyperplasia and degeneration in all their permutations and combinations. While fibro-adenoma is considered by many to be a part of the picture of cystic disease, it is not so included in this article.

In this review of the literature, therefore, the designation "cystic disease" will replace the following commonly encountered terms: Reclus'

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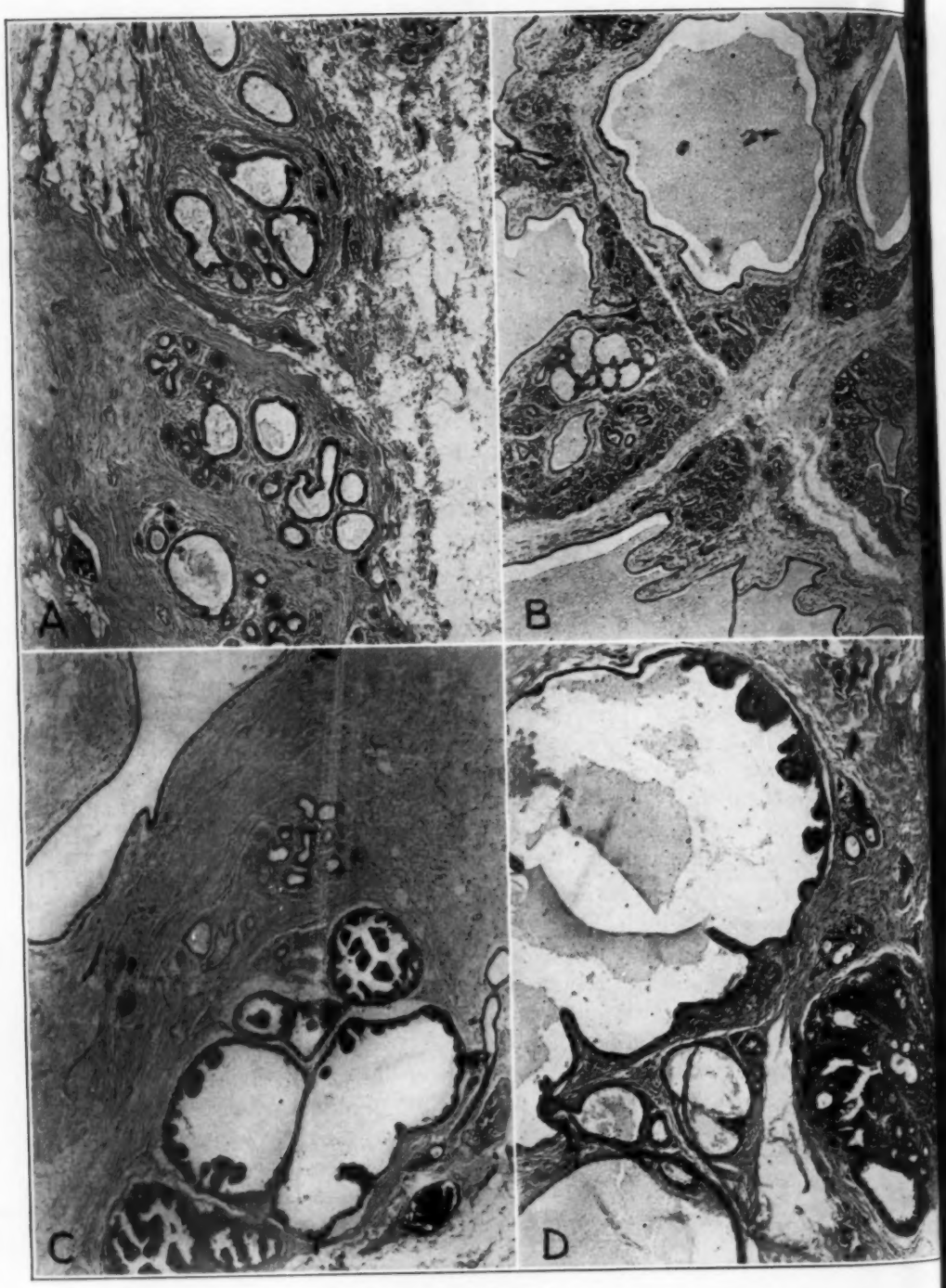
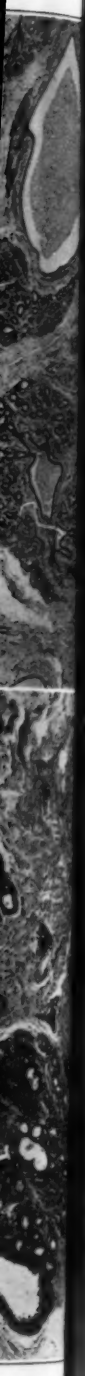


Figure 1



EXPLANATION OF FIGURE 1

Fig. 1.—*A* (case 95, series I, group A), specimen from a woman aged 30, with simple cystic disease. There were no other masses in either breast. There is simple dilatation of the ducts. No epithelial hyperplasia is seen. The patient was well without recurrence four years after local excision. *B* (case 189, series I, group A), specimen from a woman aged 33, with simple cystic disease. There were no other masses in either breast. The large ducts are greatly dilated and there is some dilatation of the smaller ducts. There is no epithelial hyperplasia. There was no recurrence six years after local excision. The patient had two pregnancies after the operation. *C* (case 17, series II, group A), specimen from a woman aged 43 with simple cystic disease. This shows a group of acini of sweat gland type occurring in simple cystic disease. The presence of this type of glandular structure is not considered in separating the groups into simple and adenocystic types. The patient was well without recurrence three years after simple amputation. *D* (case 2, series I, group B), specimen from a woman aged 36 with sweat gland cystadenoma. There were no other masses in either breast. Cysts lined by acidophil cells are present. Grade I adenocystic disease was found in other parts of the excised tissue. The patient was well without recurrence seven years after local excision.

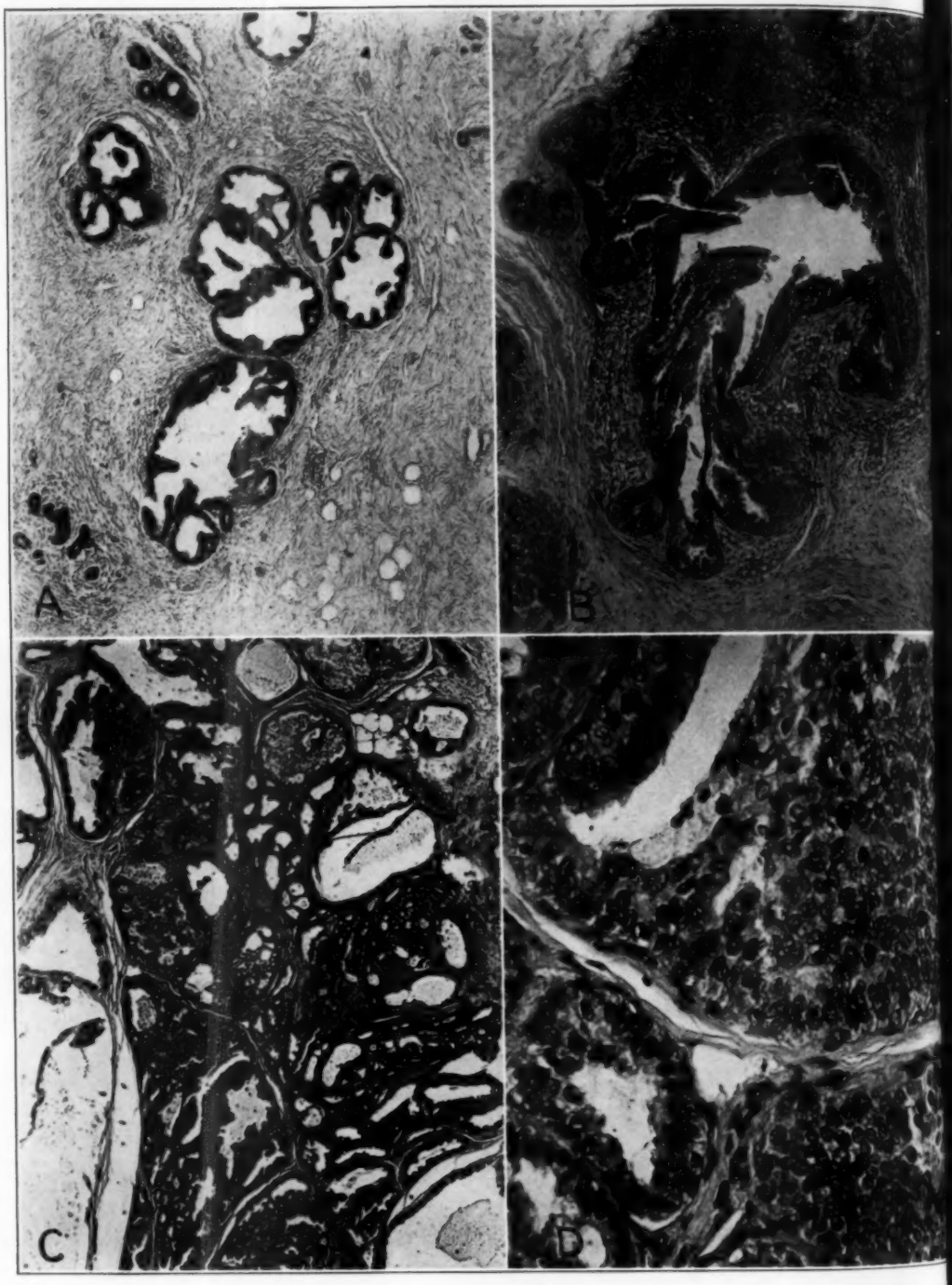


Figure 2

EXPLANATION OF FIGURE 2

Fig. 2.—*A* (case 22, series I, group B), specimen from a woman aged 37 with adenocystic disease, grade I. There were no other masses in either breast at the time of the operation. Another mass developed in the same breast two years later and was not excised. The patient died five years after the operation from a malignant condition probably originating in the pelvis (see detailed report in the text). The ducts are dilated, and there are papillary ingrowths in their lumens. *B*, specimen from Mrs. M. R., aged 50 (see text for history of case), with adenocystic disease, grade II. She had a brownish discharge from the nipple for one month. A local excision was done in 1926 under the diagnosis of adenocystic disease; there was a recurrence in four months; radical amputation was done elsewhere following a diagnosis of carcinoma; the axillary nodes were not involved. The ducts are solid and there is extension beyond the basement membrane. The patient is living and well six and a half years after the last operation. *C*, specimen from Mrs. N. H., aged 39 (see text for history of case), with adenocystic disease, grade II (border-line tumor). There was a localized mass in each breast. An area of cystic disease had been removed from the left breast five years previously. There was marked epithelial hyperplasia with papillary ingrowths—intracystic papillary cystadenoma. A diagnosis of carcinoma was made from a frozen section, and radical amputation was performed. The axillary nodes were not involved. After study of paraffin sections, the diagnosis was changed to adenocystic disease. The patient is living and well four years after the radical operation. *D*, higher magnification of an area shown in figure 2 *C*.

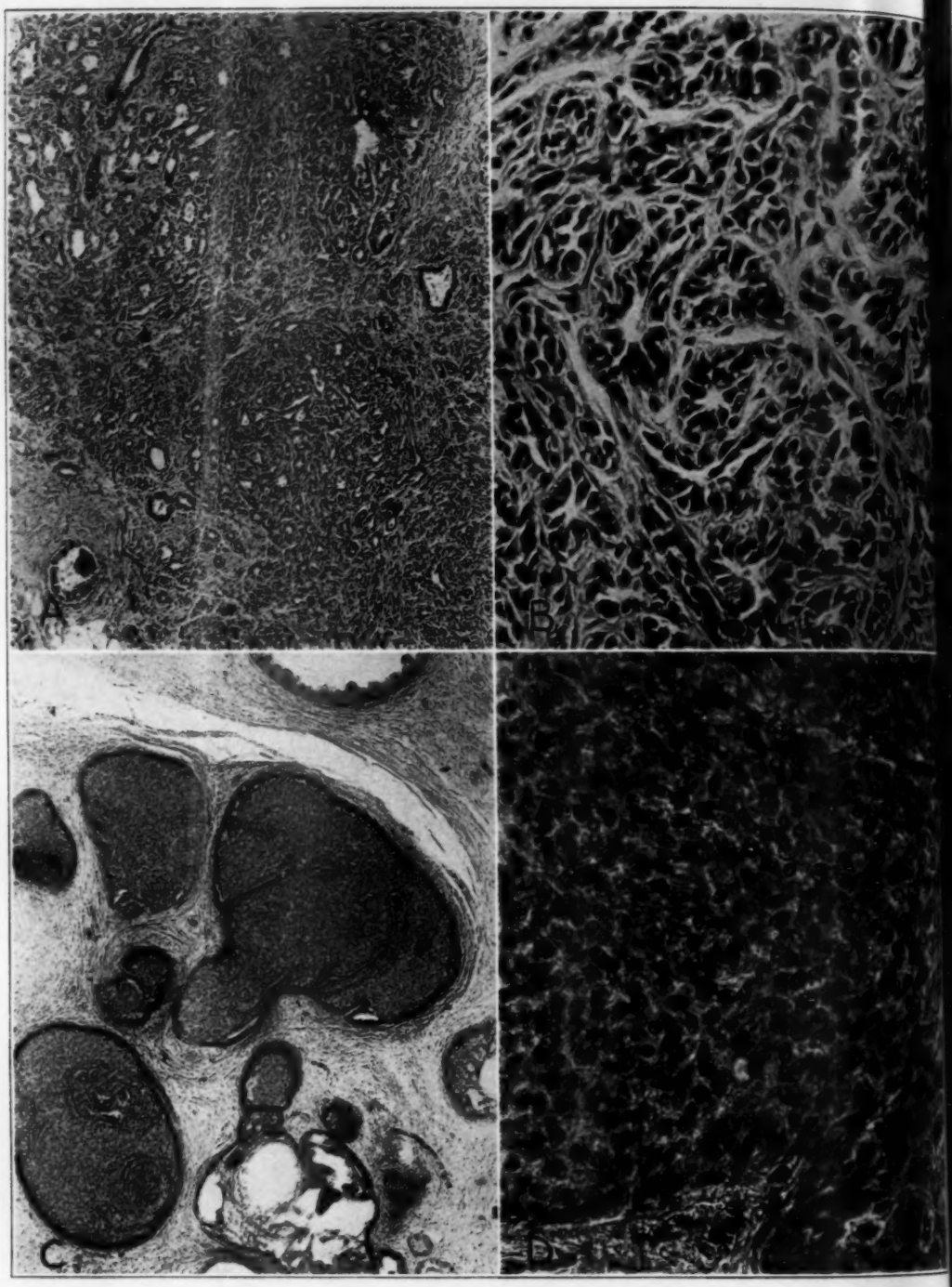


Fig. 3.—*A* (case 10, series I, group C) specimen from a woman aged 21 with adenocystic disease, grade II (border-line tumor). There were no other masses in either breast. Marked epithelial hyperplasia of lobular distribution is seen. The patient is well, without recurrence, three years after the local excision; she has married and has had two pregnancies. *B*, adenocystic disease, grade II. This is a higher magnification of an area shown in *A*. Differentiation from carcinoma is difficult under high magnification. *C* (case 2, series I, group C), specimen from a woman aged 34 with adenocystic disease, grade II (border-line tumor). No other masses were found in either breast. Under low magnification a definite lobular arrangement is noted; the ducts are filled with solid epithelial masses. The patient is well, without recurrence, ten years after local excision. *D*, adenocystic disease, grade II. This is a higher magnification of the section illustrated in *C*.

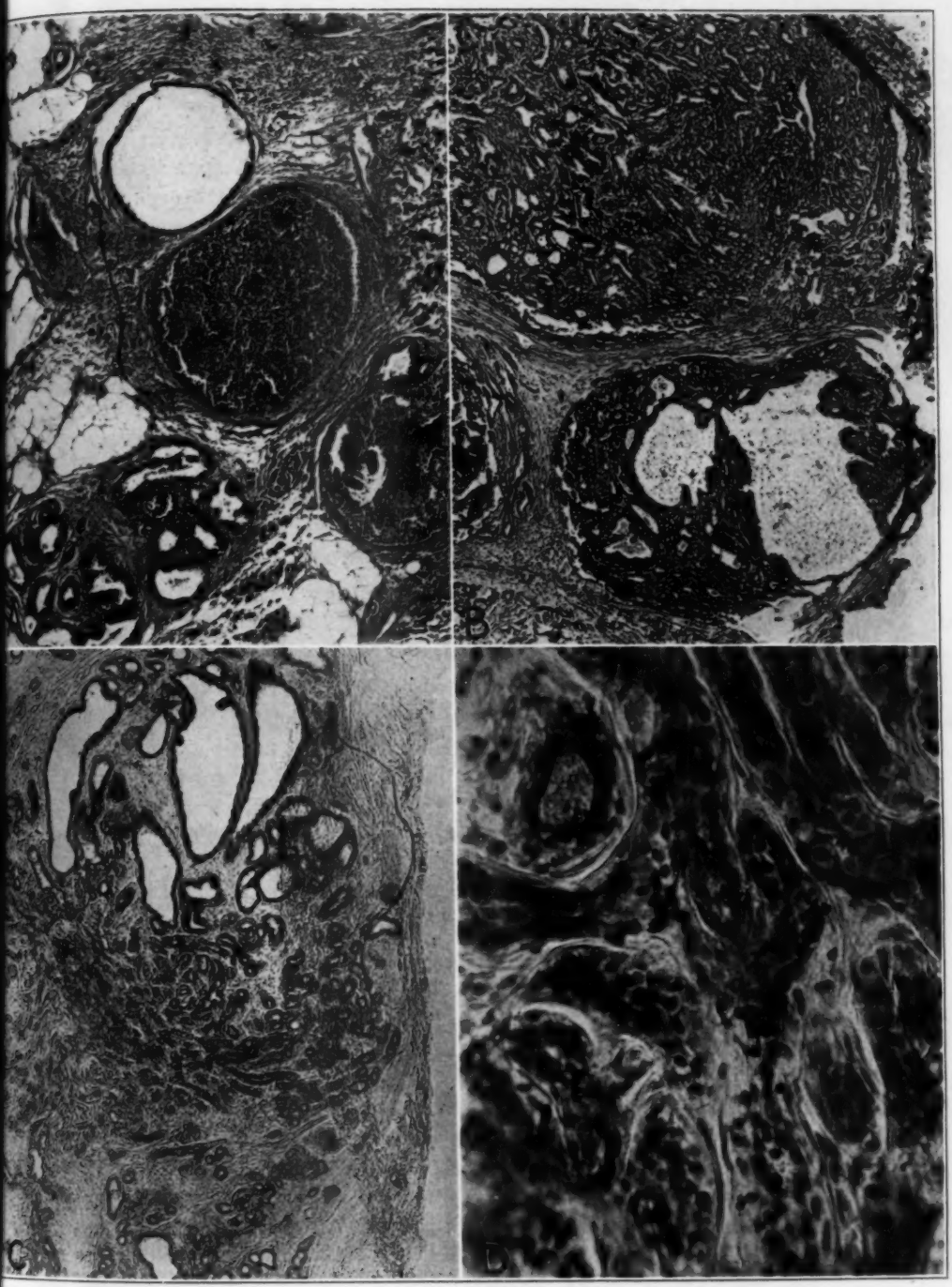


Fig. 4.—*A* (case 11, series I, group C), specimen from a woman aged 36 with adenocystic disease, grade II (border-line tumor). No other masses were found in either breast. Marked intracystic papillary growth is seen. The patient is well, without recurrence, five years after local excision. *B*, adenocystic disease, grade II. This is a higher magnification of the area shown in *A*. *C* (case 6, series II, group C), specimen from a woman aged 36 with adenocystic disease, grade II. Multiple masses were found in the breast. Adenomatous hyperplasia of lobular distribution is seen. A simple amputation of the opposite breast was performed two years before. The patient is well, without recurrence, eleven years after simple amputation. *D*, adenocystic disease, grade II. This is a high power magnification of the solid alveolar area shown in *C*.

disease, mastitis chronica cystic (König), cystadenoma mammae (Schimmelbusch), abnormal involution (Warren), senile parenchymatous hypertrophy (Bloodgood), épithéliome intra-acineux kystique (Brissaud), polykystoma épithéliale (Sasse), hydrocystoma mammae (Krompecher), lésions scléro-kystiques (Masson) and secondary epithelial hyperplasia (MacCarty).

The term "simple cystic disease" is applied to forms in which epithelial activity is limited in degree or altogether absent (fig. 1 *A* and *B*). The term "adenocystic disease," adopted by Bell, is applied to types of the disease in which epithelial hyperplasia forms a prominent part of the picture or entirely dominates it. For the purpose of designating the degree of this hyperplasia, the terms "adenocystic disease, grade I" (fig. 2 *A*), and "adenocystic disease, grade II" (figs. 3 *A*, 3 *C* and 4 *A*), are used.

REVIEW OF THE LITERATURE

It is found convenient to divide the various contributions roughly into groups according to the period and according to the views held concerning the etiology of the disease.

Early Period.—Early writers apparently either took little notice of cysts of the breast or regarded them with complacency.

Cooper and Warren (1837) described single and multiple cysts which they termed "hydatid cysts." They did not, however, confuse them with cysts of true echinococcic origin. These hydatid cysts were regarded as benign and treated by puncture or incision and occasionally by amputation.

Velpeau, in his book on diseases of the breast, also considered cysts benign and recommended nonoperative measures or only the most simple procedures such as puncture, injection of iodine or incision followed by application of an iodine pack to the cyst wall.

Paget, Brodie, Birkett, and Gross described serous cysts and cysts containing papillomas. Both types were regarded as benign, although their occasional association with cancer was noted. Probably, since Gross found that cysts constituted only 2 per cent of his group of tumors of the breast, these men recognized and described only the larger and clinically obvious types. It is to be observed that, while familiar with the microscope and its application to surgical pathology, they still relied mainly on their own clinical experience in the diagnosis of questionable lesions.

In his introduction to "Diseases of the Breast," Velpeau protested bitterly against the use of the microscope as the final arbiter in the diagnosis of lesions of a doubtful nature. Lesions which experience had shown him to be benign were labeled malignant on histologic study.

With the growing use of, and greater dependence on, the microscope ideas began to change, and much of the security which surgeons had felt in regard to cysts in the breast was lost.

While Billroth did not consider cysts dangerous, he nevertheless included them when he recommended the extirpation of all tumors.

Reclus, whose great contribution to the literature in 1883 was the excellent clinical description which finally established the disease as an entity, found his clinical impression of its benign nature at variance with impressions gained from histologic study. In advising total extirpation of the breasts he was admittedly influenced by Brissaud (1883), who published a detailed description of the histologic character of the disease and who thought it similar to cystadenoma.

Five years later (1888), having observed that his patients remained well, without the advent of malignancy, Reclus wrote that he had returned to his original clinical impression that the process is benign and had ceased doing amputations, except in older women, in whom the danger of cancer is greater.

In a symposium held in Paris in 1888, Brissaud, Trelat, Quenu, Terrier and Terrillon affirmed their faith in the benign nature of cystic disease. Sicre stated that, as a rule, the process is benign, but as he had histologic evidence that it may become malignant, he recommended amputation in older women.

Etiology.—At about the period referred to, interest in the etiology of cystic disease began to take a prominent place in the literature.

In 1892 Schimmelbusch, who occupies much the same position in the German as Reclus does in the French literature, published the results of his thorough clinical and microscopic researches. His cases, demonstrating diffuse and bilateral involvement with the nonencapsulated cystadenomatous type of cystic disease, were considered by him as proof of the neoplastic origin and nature of the process. Bilateral ablation was advised for older women, but recognizing the long chronic course of the disease, and implying an evolution into cancer only in later years, he considered it justifiable to follow a policy of waiting in the treatment of younger women. He was the first to collect a considerable number of cases of cystic disease. In 3 of 45 cases in which an operation was performed, carcinoma was demonstrated microscopically.

Tietze, in 1900, regarded the process as neoplastic. While the lesion must be considered as a primary disease of the epithelium, distinct and apart from carcinoma, the malignant stage is but a short step ahead. Such a transformation occurred in 10 per cent of his cases. Four years later he reported his investigations on senile breasts and concluded that since the epithelial changes typical of cystic disease were found in 25 per cent of older women, the predisposition to malignant tumors in such women was to that degree established.

König expressed his long held view that cystic disease is not neoplastic in origin but is a result of a chronic inflammatory reaction. The cellular infiltration and frequent axillary lymph node hyperplasias were cited as evidence of this explanation. However, König regarded carcinoma as of more frequent occurrence in breasts with the disease than in normal ones.

Delbet (1893) agreed with König. He believed that infection gained access to the breast through the ducts. As added evidence of the inflammatory nature of the disease, he emphasized the important fact that in contrast to true neoplasms, which are disturbing and deforming to the architecture of the organ, cystic disease does not disturb the lobular arrangement of the breast. While agreeing that cancer is more likely to develop in a cystic than in a normal breast, he did not believe amputation to be indicated and preferred to excise the mass locally.

Samelson believed that the evidence favors inflammation as the cause of the disease, but was unable to understand the way and sequence in which the changes were produced.

Syms and Masson, somewhat later, accepted the theory of inflammatory origin. The former believed that the disease is frequently followed by cancer and recommended radical amputation. Masson, who accepted the theory only because it was the most simple, considered that papillary forms are metaplastic and precancerous. Metaplasia, however, does not occur until cysts are formed by inflammatory constriction of the terminal ducts.

Roloff and Sasse occupied a middle ground with respect to the neoplastic or inflammatory origin of cystic disease. According to Roloff, the intimate relationship between connective tissue and epithelium precluded any great activity of the one without a like activity of the other. He likened the formation of cysts to the production of bronchiectasis. In order to be sound, any theory explaining the origin of cancer must, in his opinion, include the factor of irritation.

Lichtenhahn and Saar saw no causal relationship between any inflammatory process and epithelial overgrowth. They believed that cystic disease is a primary epithelial hyperplasia from which cancer is certainly more likely to develop than from normal resting epithelium. The diffuse nature of the process argued against its being considered a real tumor. This characteristic influenced Saar to perform amputations since after simple excisions the remaining mammary tissue always showed the disease even though only microscopically.

According to Theile, the process is neither neoplastic nor inflammatory, but degenerative. From this degeneration, however, neoplastic processes such as fibro-adenoma, sarcoma and papillary cystadenoma may develop. All the stages from the initial formation to the final production of cancer can be demonstrated. Obviously he did not consider

the occurrence of malignant tumors to be very frequent, for he recommended simple excision for localized lesions. For the bilateral, multiple and diffuse processes, in the absence of clinical signs of malignancy, he advised nonoperative measures.

Mintz (1899), Berka and Todyo believed that proliferation of connective tissue is responsible for the production of cysts.

Cornil and Bertels likewise believed that the origin of the disease lies in the connective tissue. The development of cystic changes is aided by stasis, desquamation and, eventually, dilatation. They differed as to the final outcome, the former believing that the process remains benign, and the latter, that the epithelial proliferation continues without any sharp demarcation into cancer.

Robinson believed that there is a causal relationship between the formation of cysts and malignant growth and that cystic disease of the breast should be subjected to radical removal.

Ellis reported a case of cystic disease in which he considered that malignant degeneration had occurred.

Landau thought that cystic breasts were too often amputated because of groundless fear on the part of the patient or physician.

Williams, checking over his experience, was certain that malignant change was less likely to develop in nonmalignant tumors than in normal mammary tissue.

Abbe recommended puncture as a curative measure and Bull advocated puncture followed by excision if the cyst returned.

Sheild and Williams advised puncture or incision with packing in suitable cases. For multiple cysts, multiple puncture or mammectomy was advised.

Stewart criticized Abbe for advocating puncture, since the nature of the fluid is not an index of the character of the pathologic process.

Keibel, Clark and Upcott practiced simple excision, except for diffuse or bilateral lesions, in which case Upcott believed that amputation should be done.

In 1905, Greenough and Hartwell reported their study of 30 cases of cystic disease. Since carcinoma was found in 3 cases, they concluded that the subcutaneous removal of the entire breast was indicated.

In 1907, Greenough and Simmons found an incidence of 15 per cent of carcinoma in 20 cases of papillary cystadenoma. In this special form of the disease they recommended the complete removal of the process. In some cases this could be accomplished by local excision, while in others it required amputation.

The Sweat Gland Adenomas.—The presence in the breast of glands which resemble certain large sweat glands normally found in the axilla, on the sides of the face, in the groins, on the labia majora and around the

anus attracted considerable interest and speculation regarding their relationship to the pathologic process. These glands in the breast, with large, faintly-staining eosinophilic cells often lying on a layer of smooth muscle, the "myo-epithelium," were first described by Creighton, who regarded them as the source of all forms of mammary tumors, including cysts. He believed that they represented a "reversion" to a common embryologic order.

Krompecher referred to these sweat gland types as composed of *Blassen* epithelium and related them to normal types of sweat glands found elsewhere in the body. In the breast they were considered as reversions or atavistic changes. While the proliferation of these cells lags behind that of cylindric epithelium and rarely dominates the picture, they nevertheless take a prominent part in carcinomatous proliferation, in which they transform themselves into polymorphous epithelial cells occurring in sheets.

Herzenberg supported Krompecher's views on the origin of these glands, but found it impossible to satisfy herself that cysts develop through metaplastic transformation as was suggested.

Ewing mentioned cases of carcinoma arising from the sweat gland type of epithelium within the breast.

Masson described the appearance as "metaplasie idrosadenoïde" and believed it to be a true metaplasia rather than an inclusion or defective development.

Corsy agreed with Masson, the appearance being explained as a reversion or metaplasia from the more highly developed type of secreting cell. He suggested that these glands may arise on the basis of a disturbed physiologic process and may disappear completely after lactation.

Delbet (1927) pointed out that they are too constant a finding to be explained on the basis of developmental malformation, and, like Corsy, he linked their origin with a physiologic disturbance. Both believed that while carcinoma is more likely to develop in a breast containing the sweat gland type of epithelium than in a normal breast, the likelihood is not great enough to justify their recommending amputation.

According to Peyron, the common origin of the breast and sweat glands is a sufficient explanation for all structural changes.

Goldzieher and Kaldor considered it unnecessary to resort to a theory of metaplasia to explain the presence of these glands, since metabolic disturbances of the acinar epithelium produce changes that are morphologically identical.

A reviewer of these opinions is left with the impression that whatever the origin of these distinctive types of glands and cells is, they are incidental and play no part in the course of cystic disease. They are definitely not precancerous.

Involution and Physiologic Changes.—The possible influence of physiologic stimulus and of senile and presenile involution on the development of cystic disease has long been observed.

Langhans and Billroth demonstrated the manner in which cysts were formed by the breaking down of intervening septums and the fusion of small involuting cysts.

Creighton, in his work on the mammary gland of dogs, commented on the possible effect of the periodic stimulation "evolution" and regression "involution" on the production of a pathologic process within the breast.

According to Stiles, epithelial stimulation is brought about by hormones originating in the pelvis. Nonoperative measures were advised, since the disease was not considered precancerous.

Syms called attention to the variations in the histologic picture depending on the stimulus then acting. Following lactation, a defective process of involution so commonly leaves an appreciable amount of glandular tissue, persisting in the senile breasts, that Berka believed that the absence of such residual lactation acini is a reliable indication that the patient was never pregnant.

In 1917 McFarland, collaborating with Deaver, attributed the presence of all cysts, in all age groups, to senile or presenile involution. In 1922, he elaborated on this theory to include all the forms of cystic disease. He expressed disbelief in the existence of the diffuse cystadenoma of Schimmelbusch, considering it merely one variation of the process of involution in which residual lactation acini appear in various conditions of retrogressive change. Intracystic papillomas were explained as remnants of broken-down septums. He stated that the process is harmless and has no significance with respect to the subsequent development of carcinoma. In 1927, he brought out the fact that there are localized variations in the response to hormonal stimulation. He exonerated fibro-adenoma as well as cystic disease from any responsibility in the production of carcinoma.

The relationship between the ovaries and the various stages of mammary activity had been recognized and referred to, directly or indirectly, by various early writers. The well controlled and scientific work of a few investigators on the specific hormones in relation to the cyclic changes in the normal breast stimulated fresh interest and speculation concerning their possible etiologic association with cystic disease.

Loeb (1917) and his co-workers showed the effect on the breast of corpus luteum and follicular hormone and worked out the cyclic changes in small experimental animals.

Rosenberg was the first to work out the cyclic variations in the human breast and to coordinate them with the cyclic change in the ovaries.

He found that in each premenstruum, coincident with an active corpus luteum, the terminal ducts show budding outgrowths of epithelium. At first these are solid, but later they become vacuolated to form acini. Toward the end of the period the acini begin to degenerate and eventually disappear completely. During this stage the corpus luteum shows hemorrhage and evidences of cessation of function. In the intermenstrual period only the ducts are present.

Ernst substantiated Rosenberg's observations. Dieckmann, on the other hand, while confirming the presence of a cyclic change, failed to find complete regression of lobular structures in the intermenstruum. Lobules disappear only after prolonged amenorrhea. Rosenberg's observations are explained on the basis of the youth of his patients, since the full capacity to form acini is not acquired until the age of 20. Connective tissue, as well as epithelium, participates in the change. The clinical observations of fulness and distention in the premenstruum are explained on the basis of lobular edema and are not, as Rosenberg contended, due to epithelial activity alone.

Moszkowicz, confirming in general the work of his predecessors, was impressed with the similarity between the normal proliferating lobule of the premenstruum and fibro-adenoma. In his opinion there is a causal relationship between menstrual disorders, benign diseases of the breast and, later, carcinoma. Since any mastopathy may result in malignant degeneration, he advises the removal of areas of cystic disease or the treatment of such areas with roentgen rays.

Dietrich explained the beginning of cystic disease as an evolutionary process initiated by hormones but with an atypical proliferative response. The further development is concerned with connective tissue and epithelial hyperplasia, irritation and, eventually, the formation of benign and malignant neoplasm.

Ingleby believes that fibro-adenomas arise from normal or abnormal proliferation followed by incomplete regression. If secretion without absorption occurs, cysts develop. All the variations of cystic disease can be explained on the basis of variations in the amount of epithelial proliferation and degeneration, the quantity of secretion poured into the ducts and the degree of growth and regression of the pericanalicular fibrous tissue.

Clairmont explained cystic disease on the basis of an endocrine disturbance and stated that the lively process of intermittent change makes the breast a favorable site for cancer.

Cheatle (1928), whose works will be reviewed later, said that cystic disease is really a physiologic process which has become pathologic. The views of Corsy and Delbet, that abnormal physiologic stimulation may produce a sweat gland type of epithelium, have already been given.

Orbach and Moriconi advanced the unconvincing hypothesis that cystic disease is produced by a disturbance of endocrine hormones, which is in turn produced by tuberculosis.

Konjetzny believed that in cystic disease he was dealing with presenile involution which could often be traced to disturbances affecting the menstrual cycle. Malignant changes were found in from 30 to 50 per cent of his cases. He recommended excision of the tumor mass in young persons, but advised amputation in elderly women and in patients showing diffuse involvement.

Goens-Rosales found a high percentage of active epithelial proliferation in the breasts of women between the ages of 40 and 95 who had died of conditions not originating in, or directly affecting, the breasts. Of 60 patients examined, 30 had cystic changes, 20 of these showing activity of the epithelium. Precancerous changes were found in 7 of the 20.

Borchardt and Jaffe examined both breasts of 100 women over 40 years of age. Microscopic cysts were found in one breast in 90 per cent of these and in both breasts in 70 per cent. The relation to sexual function is apparent. The disease is twice as common in nulliparous women as in women who have borne children. While the incidence of carcinoma is not as high as some place it, these writers believe that radical amputation should be done in all women over 50. In younger women conservative treatment is recommended.

In contrast to Warren, McFarland and others who stated that the entire process of involution is regressive, Oertel showed that, paradoxical as it may seem, structural and functional decline and loss are associated with proliferation of regressing cells. This occurs in the parenchyma as well as in the stroma, and with such startling frequency in the breast and prostate of elderly persons that if the condition were to be diagnosed as cancerous the majority of these organs would show in one place or another some stage of developing carcinoma. He considers these proliferative changes potentially malignant.

According to Joel, degenerated epithelium reacts differently to stimulation by ovarian hormone than normal epithelium does. He believed that malignant degeneration is a frequent occurrence in cystic disease. While fibro-adenomas rarely lead to cancers, it is better to remove them. As roentgen rays have a somewhat selective action on intracystic epithelium, they may have considerable value in the treatment of cystic disease.

Keynes and Fischer, holding similar views as to the origin of cystic disease, mentioned a constant secretion and absorption in the nonlactating glands. Interference with absorption leads to retention, irritation, hyperplasia of epithelial and connective tissue and, eventually, formation of cysts. Fischer found a high percentage of carcinomas in his cases

of cystic disease. While Keynes did not commit himself as to any causal relationship, he expressed the belief that in the present state of knowledge it is better to deal radically with the disease.

It may be pertinent to mention here some experimental work on the relationship of ovarian hormone to tumors of the breast and specifically to cancer.

Loeb, in 1919, and Cori, who repeated Loeb's work in 1927, showed the effect of castration in preventing the development of spontaneous cancers of the breast in a strain of mice which have an established incidence. If the ovarian hormone is withdrawn early in life (under 22 days), before the breast becomes well developed, spontaneous tumors do not occur. If the hormone acts for an intermediate period (from two to four months), the incidence is reduced but not eliminated. If it is allowed to act longer (from six to seven months), the usual incidence, which in Cori's strain was 78.5 per cent, occurs.

In connection with theories explaining cystic disease on the basis of obstruction to the ducts, Harris has performed some interesting experiments. He tied off and inverted the main ducts in the breasts of 7 dogs. In all cases he succeeded in obtaining high degrees of epithelial hyperplasia which, in places, even broke through the basement membrane into the connective tissue. No metastases developed, but Harris called attention to the fact that metastases are slow to occur in cases of carcinoma of the canine breast.

Yamagiwa and Murayama succeeded in producing 23 cases of cancroid tumors by injecting compounds of tar and tar derivatives into the breasts of 188 rabbits. Metastases occurred in only 1 of these; in all the others the tumors spontaneously disappeared.

The Evolution of Cystic Disease.—The literature contains many references to a sequence of events in which simple cystic processes in the breast gradually assume more and more hyperplastic forms, passing imperceptibly into benign and eventually into malignant neoplasms. Theile, Bertels and Dietrich have already been mentioned as expressing this idea.

Cheatle (1930), who has done a large amount of research, chiefly from the histologic standpoint, described such a process of evolution in detail. Beginning with what he termed "desquamative epithelial hyperplasia," in which cysts are formed, the process may pass gradually into stages of benign and finally malignant hyperplasia. The term "neoplasia" was coined to indicate the latter stage. He drew an analogy between this and the stages in the development of experimentally produced tar cancer in the skin of mice (1925). The progress may be arrested in any stage, but according to Cheatle its complete evolution into cancer accounts for 20 per cent of all carcinomas of the breast.

Cutler (1932), who collaborated with Cheatle (1930), supports this view. In his own publications he stated that 20 per cent of carcinomas develop from cystic disease. These authors regard localized nodularity as a significant clinical sign which requires histologic proof of its innocence. Large cysts, while rarely malignant, are better excised. In cases of diffuse distribution or multiple cysts amputation is advisable.

Ewing, who reported pronounced precancerous changes or miniature carcinomas in 50 per cent of breasts excised for cystic disease, believes that many cancers do not represent wholly new growths but are the result of steadily increasing epithelial overgrowth affecting, not embryonal or misplaced tissue, but the normal adult glandular epithelium. In this respect he supports Cheatle's view.

He differs from Cheatle, however, in his statement that carcinomas so arising usually appear early and dominate the picture. When cystic disease has passed a critical period, it tends to maintain a benign course over many years.

Davis followed Cheatle's teachings. He believed that limited operations should be performed on patients under 35 years of age, while in those over 35, amputation is considered to be the safer procedure.

Askanazy (1925) found a definite relationship between cystic disease and carcinoma. This is particularly true in papillomatous cystadenomas in which the genetic relationship can often be proved topographically.

Bartlett considered cystic disease as a clinical entity showing a variety of histologic pictures. It is neither a new growth nor a precancerous lesion. The same picture, minus gross hypertrophy, is seen in normal breasts. Papillomatous cysts, however, show a tendency toward malignant change and should be excised. The inability to differentiate between blue-domed cysts and papillomatous cysts makes it advisable to explore all such lesions. He found 1 case of cancer associated with blue-domed cyst.

At the Mayo Clinic, MacCarty spoke of primary, secondary and tertiary cytoplasia. Primary cytoplasia with regularly layered epithelium corresponds to what I have designated as simple cystic disease, while secondary cytoplasia, showing epithelial hyperplasia with a disturbance in the regular arrangement, corresponds to adenocystic disease. In contrast to secondary cytoplasia in which the epithelium, regardless of its activity, is confined within the limits of the lobules, the tertiary stage shows infiltration of connective tissue and is malignant. No treatment is indicated for the primary type; for the secondary type wide local excision is advisable for patients under 35 and simple amputation for those over 35 years of age.

Irrespective of etiologic considerations, many authors report definite opinions on the debated relationship.

Sistrunk was uncertain of the existence of any such relationship. Radical amputation was never advised unless the clinical signs of malignancy were present or unless the presence of carcinoma had been proved by microscopic examination.

In 1920 Rodman pointed out the frequent occurrence of cancer in cystic disease and advised radical amputation except in young women. Ten years later he receded from the position that cystic disease is precancerous and advised conservative operative measures.

Colucci, making a detailed histologic study, found carcinoma in such a high percentage of cases that he recommended radical amputation in all cases of cystic disease.

Buonsanti was disturbed by the high incidence of precancerous changes revealed by microscopic study of clinically benign types, but made the pertinent statement that only an investigation of the late results shows whether limited intervention or the radical operation is indicated.

According to Morpurgo, 24 per cent of the carcinomas originate from cystic disease. Semb, who divided his cases into two groups, found carcinoma in 24 per cent of the group in which definite hyperplasia existed. For the simple type he recommended no treatment, but for the hyperplastic type and for the patients with a bloody discharge, he urged simple amputation.

A similar division was made by Kilgore (1928). The occurrence of carcinomas in the more productive type of the disease is sufficiently high to warrant amputation.

Hellwig was likewise able to determine from microscopic examination cases in which carcinoma is most likely to develop. In his opinion 90 per cent of the amputations performed are unnecessary mutilations.

Kozhevnikoff subscribed to the opinion that malignant degeneration is fairly frequent, and cited the occurrence of carcinoma in 7.5 per cent of 80 patients with cystic disease whom he had treated. He advised mammectomy in older women. Of 26 patients treated by roentgen rays, a few were permanently relieved of symptoms.

Goldzieher likened the proliferative type of cystic disease to cirrhosis of the liver. Extensive hyperplastic vegetations are not easily distinguished from neoplasms. Both cirrhosis and cystic disease predispose to carcinoma.

The frequency of cystic disease of microscopic proportions in association with clinical or frank carcinoma is commented on and in some cases forms the basis for conclusions concerning a causal relationship.

Billroth, Ewing, MacCarty, Cheatle, Langhans and others have mentioned this frequent association. Fischer found cystic disease in 14 per cent of 151 cases of carcinoma. According to him, the cystic changes in these cases were primary and the carcinoma secondary. Semb found

an incidence of 55 per cent and Junge one of 83 per cent for the association of cystic disease with carcinoma.

The presence of cystic disease around the site of a carcinoma was explained by Keynes as due to an irritation produced by the carcinoma. He quoted Drew who, by cultural methods, demonstrated the presence in cancers of a growth-activating substance capable of strongly stimulating the growth of epithelial and connective tissue.

Fraser studied whole sections of breasts removed for carcinoma. He found a high incidence of a widespread series of changes similar to certain forms of cystic disease and concluded that a local focus of malignant changes develops first and later spreads through the ducts to produce secondary changes. These spreading cells are none the less malignant, although they are confined within the ducts. Only by postulating a primary malignant focus could he explain the definite centrifugal spread of the associated changes which are always most marked near the malignant growth.

Charteris, using the same type of material, arrived at a different conclusion. In an attempt to determine what changes preceded the malignant tumor, he examined 48 whole breasts removed for cancer. All grades of epithelial hyperplasia were found, including solid sheets of cells which in places were breaking through and invading the connective tissue. Most of the changes were in the ducts, and they were present only to a lesser extent in the acini. The process may be localized or may extend diffusely throughout the breast, with breaks in the duct wall in several locations, thus verifying the multicentric origin of cancer. He was convinced that what he observed represents a long series of proliferative changes, in the final stage of which all transitional forms can be seen. While all the forms are rarely present in the same breast, the impression of their essential continuity is obtained.

Thus far in this review, except in the case of the older clinicians, the views and convictions expressed in regard to cystic disease and its relationship to cancer have largely been obtained by a study of histopathology.

An entirely new approach to the problem is offered by Bloodgood. Convinced that most cases of cystic disease never become malignant and that many needless amputations were being done, he practiced limited operations and followed his patients for years to determine the incidence of carcinoma. Thus he obtained a correlation between the various histologic pictures and the clinical course of the disease.

It is of interest that in 1904 Bloodgood, basing his opinion on microscopic criteria only, had concluded that malignant epithelial change occurred in 10 per cent of all cases of cystic disease. In 1906 he wrote that adenocarcinoma was already present in over 50 per cent of patients with the adenocystic variety of the disease whom he had examined.

In 1921, having changed his opinion, he reported his experience with 350 cases of cystic disease, in 128 of which the treatment had been local excision only. A follow-up showed that carcinoma had developed in 3 of these cases, an incidence of about 2 per cent. He concluded that, with the exception of nonencapsulated cystadenoma, or, as it is here termed, adenocystic disease grade II, cystic disease is not a precancerous lesion and cancer is no more likely to develop in a breast so involved than in a normal one.

In 1929 he amended this impression by including diffuse nonencapsulated cystadenoma among the benign lesions. He had recognized this variety of the disease in over 100 patients and treated them without operation. Malignant tumors did not develop in any of them. In the same year he reported his experience with over 300 cases in which blue-domed cyst was treated by local excision. A follow-up over a period of years showed no greater incidence of carcinoma than in women with normal breasts.

Reviewing his locally removed "border-line" tumors in 1931, he found that all of these patients, over whose diagnosis pathologists had disagreed fifteen years before, were living and well or had died of other causes without having shown evidence of cancer.

Bloodgood has therefore concluded from his years of study, combining and correlating microscopic pictures with the clinical course of the disease, that cystic disease is not a precancerous lesion.

Using the same method of investigation, but confining his attention to intracystic papillomatous processes, Hart reported 104 benign and 24 malignant cases. Of the 24 cases of malignant growths, 21 were recognized clinically, 2 were "border-line" cases, and 1 was clinically considered benign. All the patients were treated by the radical operation. Of the 104 with benign growths 38 per cent had radical amputations, 40 per cent simple amputations and 22 per cent simple excisions. Follow-up information was secured on 66. Regardless of the type of operation, all had remained well. Of the group with malignant changes 10 were followed; 7 of these died of cancer in less than five years, and the others died of causes unrelated to the malignant condition. Hart concluded that the malignant cases had been malignant from the beginning and that when the cyst wall is thin and freely movable and the base not infiltrated, the lesion is benign, regardless of the pathologic process of the papilloma.

Johnson found that of 107 cases of isolated cysts of the breast subsequent malignant tumors developed in only 2. Forty-seven cases of chronic mastitis (cystic disease) were followed, in none of which malignant changes developed. He believes that the evidence does not warrant the tendency to remove breasts for comparatively slight and indefinite lesions.

Peck and White followed their cases of benign tumors, 63 of which were examples of localized cystic disease in its various forms. In none of these did carcinoma subsequently develop.

ANALYSIS OF THE LITERATURE; COMMENT

In summarizing and classifying the aforementioned opinions it is found that while a few writers are noncommital, the majority are easily divided into two groups: those who consider cystic disease to be a benign lesion with no causal relationship to cancer, and those who believe it to be precancerous and a menace to the patient. Of those expressing definite views, twenty-three were of the former and forty-two of the latter opinion.

The treatment advised corresponds to, and in the majority of cases is consistent with, the particular view held. There are individual variations and concessions, particularly in dealing with younger women. The etiologic concept of the disease has surprisingly little influence on the molding of opinion regarding the important relationship in question. It is further noted that, with rare exceptions, those who subscribe to the precancerous theory of cystic disease obtained their data and reached their conclusions through histologic methods of research. On the other hand, advocates of the theory of the benign nature of the disease are just as consistently composed of older clinicians who express belief based on their own clinical experience, or those of the newer group who, pursuing the follow-up method of investigation, have subjected their diagnoses and prognoses to the proof of time.

Because of this close correlation one is led to believe that conclusions are practically predetermined by the method of investigation and that it is the method rather than the conclusion which merits critical consideration.

The histologic evidence invoked in favor of the precancerous theory of cystic disease may be briefly summed up:

1. Cystic disease is frequently found in association with frank carcinoma.

2. Various gradations of epithelial proliferation may exist to give the impression that cystic disease represents a progressive evolution of epithelial hyperplasia eventuating in carcinoma.

3. The examination of tissue removed from breasts containing cystic disease frequently reveals histologic pictures which may be interpreted as representing early carcinoma.

It seems established that a high percentage of frank carcinomas show associated changes characteristic of cystic disease of microscopic proportions. It is not established, however, that cystic disease of clinical proportions is frequently encountered under similar conditions. On

examination Charteris found cystic disease of microscopic proportions in the majority of 48 breasts removed for carcinoma. In only 2, however, were the changes of such a degree as to be clinically recognizable.

Recently I reviewed the cases of carcinoma of the breast in which operation was performed at the Minnesota General Hospital between the years 1916 and 1928. Of 88 cases only 4 showed a history of antecedent masses which could have represented cystic disease. In 444 cases of carcinoma Johnson found but 2 in which an antecedent history of cystic disease was obtained.

In view of the extreme prevalence of cystic disease in all age groups (Pribram, Fischer, Goens-Rosales, König, Borchardt and Jaffe, Hahn, Morpurgo and others) the failure of cystic disease to take a more prominent part in the antecedent history of carcinoma of the breast is striking and inconsistent with the supposition of a causal relationship in the occasional cases in which cancer and cystic disease of clinical proportions are found together.

MacCarty indicated the fallacy of such an assumption when he said that the coincidence of benign and malignant hyperplasia does not prove that one necessarily preceded the other.

Theile, Bertels, Dietrich, Cheatle (1930), Cutler (1932), Charteris and others constitute a group which believes in the evolution of many carcinomas through successive stages of the epithelial hyperplasia found in cystic disease. Ewing, himself a supporter of the precancerous theory, named the great weakness in this approach to the problem when he stated that in no case can one trace the evolution of suspected areas into fully developed cancer. However, Junge, Moszkowicz, Goldzieher, Bertels and Charteris believe that they have demonstrated carcinoma arising not only in one focus, but simultaneously in several different foci in the breast.

The opinion as to the multicentric origin of cancer of the breast was severely criticized by McFarland who pointed out that, except for extension by lymphatics and ducts, a carcinoma is in continuity through its whole extent. No one, he affirmed, has ever seen the beginning of a cancer. Fraser explained the escape of epithelial cells from ducts in which they have been confined, not as new foci of malignant change, but as extensions of malignant cells from the primary tumor through the ducts to establish secondary sites of carcinoma in other parts of the gland.

These contradictory interpretations of the same picture illustrate the most fundamental handicap in the use of histologic methods alone in determining the relationship between cystic disease and cancer. The lack of generally accepted diagnostic criteria for the differentiation of benign from malignant hyperplasias has resulted in the widest range

of interpretations and probably explains the high incidence of malignancy in cystic disease reported by Konjetzny (1921), Semb and Morpurgo.

Correlation between the histologic picture of a lesion and its clinical course over a period of years has enabled the diagnoses and prognoses to be made with a high degree of accuracy in the great majority of cases. There are, however, certain so-called "border-line" lesions in which this correlation has not been established. Failure to recognize these lesions or their ready inclusion with malignant growths creates a distorted impression of the nature of cystic disease which is not verified by its clinical behavior as revealed by Bloodgood (1931), Hart, Johnson and others.

I believe that the outlined basic handicaps place a limit on the information which may be obtained by purely histologic methods and that the behavior of a lesion over a period of years rather than its appearance under the microscope is the accurate index in determining its true nature. Therefore our researches should logically be directed along clinicohistologic lines.

SOURCE OF THE MATERIAL

Cases of cystic disease were obtained through the records of the department of pathology at the University of Minnesota, through the Minnesota General Hospital and from six private hospitals in Minneapolis and St. Paul. Only cases in which the original microscopic sections were available or in which the diagnosis had been made by a recognized and competent pathologist were used.

While there is no clearcut division in the degree of hyperplasia manifest in different tissues, in order to determine whether or not those showing the extremes of proliferation merit any special consideration it was thought advisable to subdivide the adenocystic group into cases of grade I and grade II, the latter showing the more marked proliferation.

I graded the cases after having examined the sections of 75 per cent. The other 25 per cent represents cases of which the sections were not available. Accepting the pathologists' diagnoses, the latter cases were distributed as follows: Those bearing only the diagnosis of cystic disease were placed with cases of simple cystic disease and those in which adenocystic disease was specified were placed with the cases of adenocystic disease of grade I. The cases in the adenocystic group of grade II are only those of which I studied the sections myself.

Follow-up information was obtained through the private physician. In many cases, however, information was sought directly from the patients. Since these were, for the most part, women who are naturally concerned about their breasts, it is considered that the information relative to recurrence or to the possible development of malignancy is sufficiently accurate to warrant their inclusion in this material.

PRESENTATION OF MATERIAL

Two series of patients who were followed up are presented: series I, composed of 233 women treated only by local excision, and series II, composed of 57 women treated by simple amputation. Since the two series are used for different purposes, they are commented on separately. In regard to etiologic factors, however, they are considered both separately and in combination.

Of the 233 cases in series I, 82 per cent were graded as simple cystic disease (group A), 12.4 per cent as adenocystic disease grade I (group B) and 5.6 per cent as adenocystic disease grade II (group C).

Of the 57 cases in series II, 73.7 per cent were graded as simple cystic disease (group A), 14 per cent as adenocystic disease grade I (group B) and 12.3 per cent as adenocystic disease grade II (group C).

Of the whole material, composed of 290 cases, 80.3 per cent were graded as simple cystic disease and 19.7 per cent as adenocystic disease.

TABLE 1.—*Age Distribution in Combined Series I and II* *

Group	20 to 24 Years	25 to 29 Years	30 to 34 Years	35 to 39 Years	40 to 44 Years	45 to 49 Years	50 to 54 Years	55 to 59 Years	60 to 65 Years	Total
A	14	18	30	45	54	41	15	3	3	223
B and C	8	4	5	12	7	9	4	3	2	54
Total cases	22	22	35	57	61	50	19	6	5	277
Percentage	8	8	12.6	20.6	22.1	18	6.9	2.1	1.7	100

* In 13 cases no age was reported.

Age.—By combining series I and II and arranging the cases in five year periods according to the age at operation, the maximum incidence (22.1 per cent) is found between the ages of 40 and 45 (table 1). This coincides with the observations of Abbe, Keynes and Bloodgood. Kozhevnikoff, on the other hand, found the maximum incidence to be under 40 years of age.

Considered in distribution by decades, the maximum incidence (40.1 per cent) is within the period from 40 to 50 years. The maximum incidence of carcinoma is within the same period (Bunts, Crile, Evans and Leucutia, Lane-Claypon, Lee, Pfahler and Widmann).

A series of 8,053 cases of carcinoma of the breast reported by Lane-Claypon and arranged in quinquennial periods according to the age at operation is used for comparison with the similarly arranged cases of this series. This comparison is graphically represented in figure 5.

It may be observed that whereas the incidence of cystic disease reaches 8 per cent before the age of 25, reaches a maximum between 40 and 45 and drops quickly after 50, the incidence of carcinoma is almost negligible until after 30, reaches a maximum between 45 and

50 and then (in contrast to cystic disease) drops slowly until advanced ages are reached. The peaks are but five years apart, demonstrating the considerable overlapping in the age distribution for the two diseases.

The theory advanced by Cheatle (1930) and others, that cystic disease starts in its more simple forms early in life and gradually, over a period of years, progresses through gradations of epithelial hyperplasia, meets with strong contradictory evidence when the age distribution for adenocystic forms of the disease is examined. It would seem reasonable, if such a theory were indeed a fact, that the maximum incidence of the adenocystic forms would be found in a higher age group

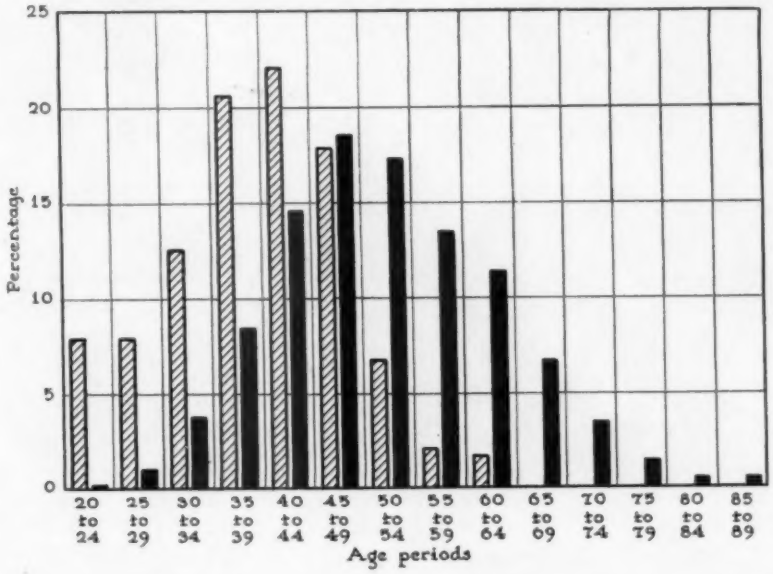


Fig. 5.—Graph showing the comparative age distribution of 290 cases of cystic disease of the breast and 8,053 carcinomas of the breast (Lane-Claypon) arranged in five year periods. The striped areas indicate cystic disease; the black areas, carcinoma.

than that of simple cystic disease. Such is not the case, however, for the maximum incidence of adenocystic disease is between the ages of 35 and 40 in contrast to simple cystic disease, which is most frequently encountered between the ages of 40 and 45. The incidence of 14.8 per cent of all cases of adenocystic disease before the age of 25 and of 22.2 per cent before the age of 30 is incompatible with Cheatle's theory. Figure 3 *A* is a photograph of a section of mammary tissue removed from a girl aged 21, and figure 6 *C* shows a section from a girl 22 years of age. Both reveal degrees of epithelial hyperplasia which, according to the aforementioned theory, should have required years to develop.

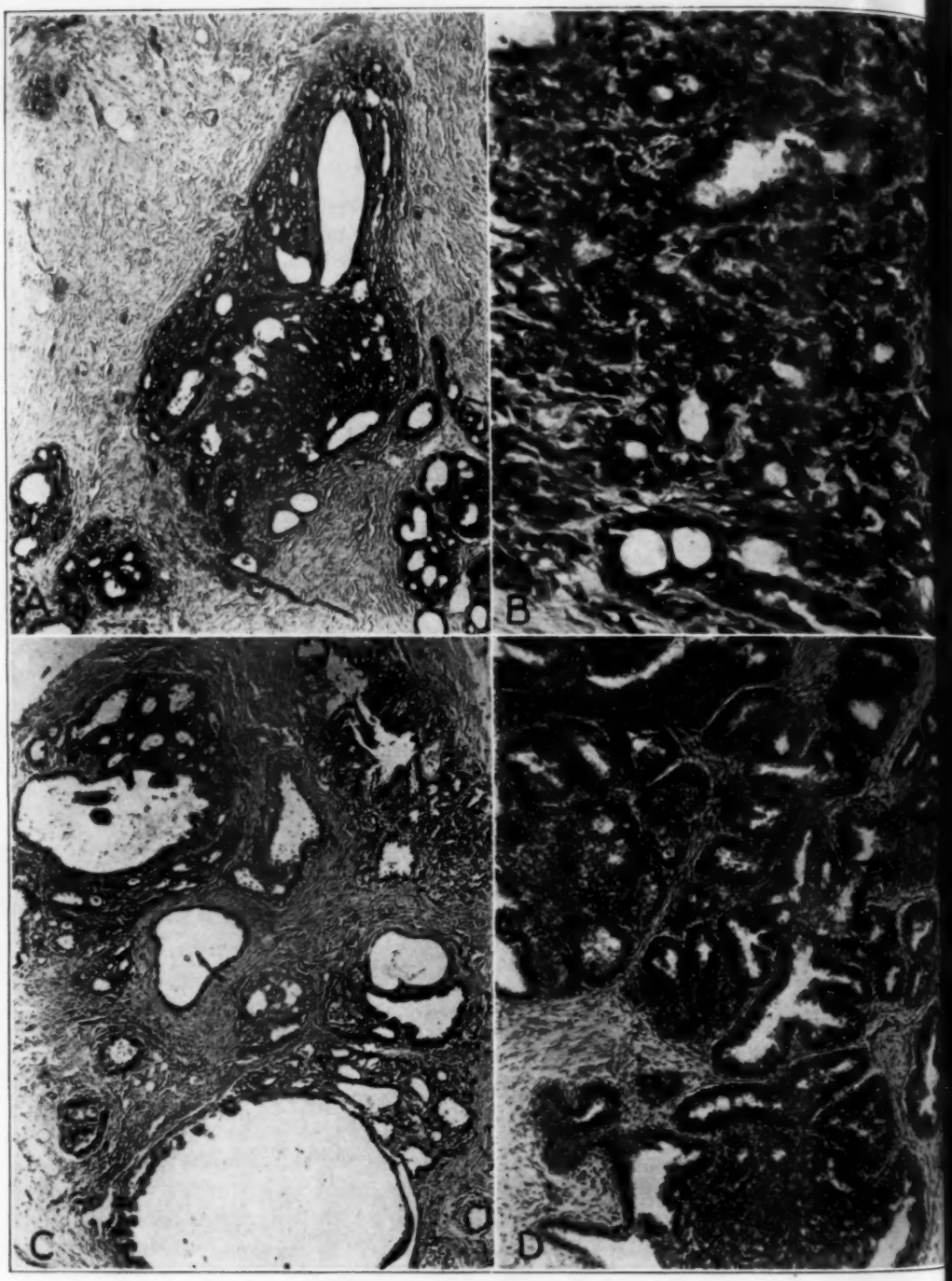


Fig. 6.—*A* (case 6, series I, group B), specimen from a woman aged 33 with adenocystic disease, grade I. No other masses were found in either breast. An adenomatous type of hyperplasia is seen. The patient is well, without recurrence, six years after local excision. *B*, adenocystic disease, grade I. This is a high power magnification of the area illustrated in *A*. At this magnification the differentiation from carcinoma is not readily made. *C* (case 1, series I, group C), specimen from a woman aged 22 with adenocystic disease, grade II. No other masses were found in either breast. Adenomatous hyperplasia and cysts, with a definite lobular distribution, are seen. The patient is well, without recurrence, three years after local excision. *D* (case 13, series I, group C), specimen from a woman aged 27 with adenocystic disease, grade II. The distribution in the breast is unknown. Adenomatous hyperplasia in lobular arrangement is seen. The patient is well, without recurrence, two and a half years after local excision.

Duration of Symptoms.—It is found that 35 per cent of all the patients reported for operation within one month, and 68.6 per cent within six months of the beginning of symptoms (table 2). There is no way of noting in what percentage of the cases of longer duration the delay represented a period of observation on the part of the sur-

TABLE 2.—*Duration of Symptoms in the Combined Series* *

	Months				Years							
	1	1 to 3	3 to 6	1 to 12	1	2	3	4	5 to 9	10 to 14	Over 15	Total
Group A												
Number.....	62	33	32	13	10	8	6	..	7	1	3	175
Percentage....	35.4	18.9	18.3	7.4	5.7	4.6	3.4	..	4.0	0.6	1.7	100.0
Groups B and C												
Number.....	14	2	6	5	4	6	2	..	..	2	1	42
Percentage....	33.3	4.8	14.3	11.9	9.5	14.3	4.8	..	..	4.8	2.3	100.0
Total												
Number.....	76	35	38	18	14	14	8	..	7	3	4	217
Percentage....	35.0	16.1	17.5	8.3	6.5	6.5	3.7	..	3.2	1.4	1.8	100.0

* In 73 cases no duration was reported.

TABLE 3.—*Marital State in the Combined Series*

	Married	Unmarried	Total
Group A.....	165	68	233
Group B.....	28	9	37
Group C.....	10	10	20
Total.....	203	87	290

TABLE 4.—*Pregnancies in the Combined Series*

	Before Operation		After Operation	
	Number of Cases of Pregnancy	Total Adequate Histories	Number of Cases of Pregnancy	Total Adequate Histories
Group A.....	78	162	10	119
Group B.....	14	26	2	22
Group C.....	3	13	2	11
Total.....	95	201	14	152

geon. Of the simple cystic cases, 20 per cent had durations of one year or over, while 35.7 per cent of the adenocystic group had shown symptoms for over one year. Six and three-tenths per cent of the simple cystic group of cases and 7.1 per cent of the adenocystic group had shown symptoms for over five years.

Marital State and Pregnancies.—Of the entire group of patients, 30 per cent were unmarried and presumably had never been pregnant (tables 3 and 4). Of 201 patients with an adequate history 95, or 47 per cent, had been pregnant before operation. Of 152 patients for

whom information on this point was available, 14 have had pregnancies since the operation. Since on the average cystic disease occurs later than the age of woman's greatest fertility, and since of this series, 30 per cent were single women, it is not surprising that there were not more subsequent pregnancies.

Kilgore (1929) showed that the actual incidence of malignant growths occurring during pregnancy is greater than the estimated incidence in any one year. In 12 cases of series I (in which only local

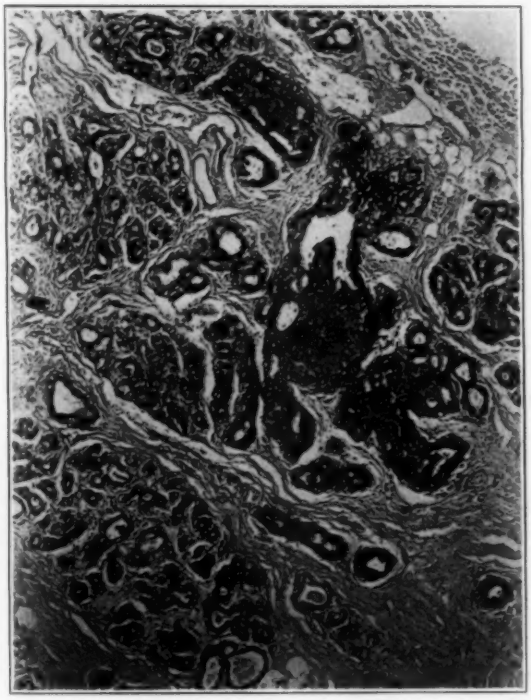


Fig. 7.—(Case 7, series I, group C), specimen from a woman aged 42 with adenocystic disease, grade II. No other masses were found in either breast. Adenomatous hyperplasia with formation of solid lobules is seen. The patient is well, without recurrence, three years after local excision.

excision was performed) the breast has withstood the strongest of all physiologic stimuli without showing development of carcinoma. The patient with a lesion (fig. 3*A*) which was diagnosed as adenocystic disease grade II, but which many would have diagnosed as malignant, has had two pregnancies since the local excision of the mass. She has remained free from recurrences or other pathologic changes in the breast.

Pain.—In cystic disease there is little correlation between the degree of pain and the nature and extent of the process (table 5). In this series pain was present in 30.5 per cent of the simple cystic group, in 31.3 per cent of the grade I group and in 33 per cent of the grade II adenocystic group.

Cheatle (1930) and Cutler described its frequent presence in the early changes of "mazoplasia." The latter reported encouraging results in the control of pain by the use of ovarian residue administered orally. He believes that the changes in the breast responsible for the pain were produced by an excessive amount of corpus luteum hormone, and that

TABLE 5.—*Pain* *

	Before	Total Adequate Histories	After	Total Adequate Histories
Group A	53	174	7	233
Group B	10	32	4	37
Group C	5	15	1	20
Total	68	221	12	290

* Six of these patients reported pain both before and after operation.

TABLE 6.—*Discharge*

	Excision Series		Amputation Series			Total Adequate Histories
	Blood	Serous	Bloody	Serous	Total	
Group A	2	2	1	..	3 bloody 2 serous	174
Group B	1	..	1	..	2 bloody	32
Group C	..	..	3	..	3 bloody	16
Total	3	2	5	..	8 bloody 2 serous	222

the administration of ovarian residue counteracts or inhibits this excessive secretion.

From the diagnostic standpoint pain is of little value. Bartlett (1921), Crile and others have found it to be present only in the late stages of carcinoma. Cheatle (1927) reported a case in which the biopsy specimen from a painful area, prior to the appearance of a mass, revealed an early carcinoma. Kozhevnikoff named pain as one of three clinical signs of cystic disease. It was present in 57 per cent of his cases.

In this series, of 55 patients who reported pain prior to operation, 6 had persistence of this symptom. Six who had not noticed pain before reported pain after the operation.

Discharge.—The significance of a discharge from the nipple, particularly of a bloody discharge, has been variously interpreted (table 6). Judd, Miller and Lewis as well as Adair have found about the same

proportion of benign and malignant lesions to be responsible for its presence. Cutler (1932) and Floyd and Haggard thought that in the majority of cases bleeding is due to small benign duct papillomas and rarely to malignancy. Hart, considering only papillary cystadenoma, found that 48 per cent of the benign and 12 per cent of the malignant cases showed discharge as the most prominent symptom. Joel stated that he had never seen malignant degeneration in his cases of bleeding breasts. Knoflach and Urban followed 40 patients with a bloody discharge from the nipple; 30 of these were operated on and 10 were not. In twenty-three years there was only 1 patient of whom they lost track. Carcinoma did not develop in any of the others. MacNeal and Cheatle (1932), on the other hand, regard bleeding as of grave significance. Pribram considers lesions which produce bleeding as intermediate between benign and malignant growths. Bloodgood (1922) and Peck and White did not operate for bleeding alone. Bleeding, according to them, is only a symptom and, occurring without a palpable tumor, does not demand treatment. Hellwig, Hart, and Floyd and Haggard performed local excisions for diagnosis and, failing to find a malignant growth, considered this procedure sufficient. The latter, however, recommended simple amputation for women over 35 and for those who cannot be closely observed after local excision. Knoflach was content with local excision in cases of discrete tumors producing bleeding, but he urged amputation in cases of breasts showing diffuse resistance.

In 1926 Erdheim believed that local excision often sufficed for the treatment of benign lesions producing bleeding. One year later he changed this opinion and recommended radical amputation.

Mintz (1899) was so impressed with the frequency of malignancy in lesions showing a bloody discharge that he performed the radical operation in all such cases.

Cutler (1929) has demonstrated a method of transilluminating the breast to reveal small sources of bleeding which would otherwise defy localization. Fray and Warren advocated stereoscopic roentgenography as an aid to localization and differentiation.

In the present series of 222 cases in which adequate histories were obtained 8 cases showed a bloody and 2 a serous discharge. Five of the 8 patients were treated by simple amputation; 1 of these died of carcinoma of the stomach one year later. The other 3 and the 2 patients with a serous discharge were treated by local excision. All remained free from recurrence, although 3 were subsequently operated on for involvement of the opposite breast.

Antecedent Treatment.—Of the 43 patients who at some previous time had had lesions in the breast, 10 had had local excisions of benign masses (fibro-adenomas and areas of cystic disease) from the same breast and 12 from the opposite breast (table 7). In 1 bilateral local

excision had been performed, and in 2 local excision of one breast had been combined with simple amputation of the other. Seven stated that they had had lactation mastitis or an abscess in the same breast. Seven had undergone a simple, and 1 a radical, amputation for benign lesions. On 3 patients the radical amputation for cancer had been performed.

Distribution of Disease Process.—The distribution of the disease in the breast, as revealed by clinical examination, was, for the sake of convenience, designated as localized, multiple and diffuse (table 8). Any single mass occupying no more than one third of the breast was called

TABLE 7.—*Antecedent Treatment*

	Excisions for Benign Lesions		Amputations for Benign Lesion	Amputation for Cancer	Mastitis and Abscesses
	Same Breast	Opposite Breast			
Group A	12	11	7	3	6
Group B	1	1	..	..	1
Group C	..	..	1	..	..
Total	13	12	8	3	7

TABLE 8.—*Distribution in Relation to Type of Treatment*

	Localized*		Multiple		Diffuse		Total of Adequate Histories
	L. E.	S. A.	L. E.	S. A.	L. E.	S. A.	
Group A	139	18	11	8	2	5	183
Group B	23	2	..	2	..	3	30
Group C	9	2	1	1	..	1	14
Total	171	22	12	11	2	9	227
Percentage	85.0		10.1		4.9		100

* L. E. indicates local excision; S. A., simple amputation.

localized. The excision of no more than one half of the breast was considered a local excision.

Of 227 patients of whom an adequate description was available, 193 (85 per cent) had localized, 23 (10.1 per cent) had multiple, and 11 (4.9 per cent) had diffuse, distribution. Fourteen of this number had bilateral localized involvement and 1 had bilateral multiple involvement. Seven of the 14 patients with bilateral involvement were treated by local excision in one breast only, and 7 underwent local excision in both breasts. Bilateral simple amputation was performed on the patient with bilateral multiple tumors.

The influence of the distribution of the disease within the breast on the type of treatment administered is indicated by the high percentage of multiple and diffuse processes in the cases of amputation.

Follow-Up Period.—Series I: Two hundred and thirty-three patients were treated by local excision (table 9). The minimum follow-up period was two years, and the maximum, fourteen years.

Of the entire series of cases, 89.2 per cent were followed three or more years, 60.4 per cent were followed five or more years, and 15.9 per cent were followed ten or more years.

Of the 190 cases constituting the simple cystic group (group A), 89.5 per cent were followed three years or more, 62.1 per cent, five years or more, and 16.3 per cent, ten years or more.

TABLE 9.—*Follow-Up by Years*

	Series I, Patients Treated by Local Excision — Years														Percentage
	2	3	4	5	6	7	8	9	10	11	12	13	14	Total	
Group A*	20	30	22	25	21	18	9	14	11	6	7	3	4	190	81.9
Group B†	2	8	1	4	4	3	2	1	2	..	2	..	..	29	12.5
Group C	3	5	1	2	..	..	..	..	1	..	1	..	..	13	5.6
Groups B and C	5	13	2	6	4	3	2	1	3	..	3	..	..	42	18.1
Total	25	43	24	31	25	21	11	15	14	6	10	3	4	232	
Percentage	10.8	18.5	10.3	13.4	10.8	9.1	4.7	6.5	6.0	2.6	4.3	1.3	1.7		100.0
	Series II, Patients Treated by Simple Amputation														
Group A	1	7	4	5	6	3	4	5	2	3	2	..	..	42	75.0
Group B	1	2	2	..	..	..	..	..	1	1	..	..	..	7	12.5
Group C	..	..	3	2	..	1	..	..	..	1	..	..	..	7	12.5
Groups B and C	1	2	5	2	..	1	..	..	1	2	..	..	..	14	25.0
Total	2	9	9	7	6	4	4	5	3	5	2	..	..	56	
Percentage	3.6	16.1	16.1	12.5	10.7	7.1	7.1	8.9	5.4	8.9	3.6	..	..		100.0
	Combined Series														
Number	27	52	33	38	31	25	15	20	17	11	12	3	4	283	

* In one case cancer developed within one year.
† One patient died one year later of carcinoma of the stomach.

Of the 42 cases constituting the adenocystic groups (groups B and C), 88.1 per cent were followed three years or more, 52.3 per cent, five years or more, and 14.2 per cent, ten years or more.

In 1 of the 233 patients, carcinoma of the breast developed within one year. The history of this case follows:

CASE 45, GROUP A.—A married woman, aged 45, who had never been pregnant but whose menses had always been regular and normal, was admitted to the hospital because of a small, discrete, unattached mass in the right breast near the nipple. Four years before, a small fibro-adenoma had been removed from the same breast, close to the site of the new tumor. On local excision the new area proved to be simple cystic disease. Seven months later a small mass was discovered in the same breast in the upper and outer quadrant near the periphery. This was excised and found to be frank carcinoma. A radical amputation was performed one month later, and although histologic examination revealed the involvement of one axillary lymph node, the patient has remained free from recurrence for three and one-half years.

Among the 233 cases, there were 4 deaths, 3 of which were unrelated to carcinoma. Two of these patients (cases 28 and 179, belonging to the simple cystic group) died five and ten years after the operation, of suicide and apoplexy, respectively. The third (case 12, adenocystic group, grade I) was followed twelve years and died, according to her physician's report, of "heart and kidney trouble." The fourth patient (case 22, adenocystic group, grade I) died of carcinoma probably originating in the pelvis. Her history follows:

She was 37 years old and unmarried. There is no record of her symptoms or of their duration. At operation a mass of ½ × 1½ inches (1,767.8 cm.) was removed from the upper and outer quadrant of the right breast. The specimen (fig. 2 *A*) was sent to Dr. Bell, who made a diagnosis of cystic disease. The area illustrated is the only portion of the section which showed epithelial hyperplasia.

After two and one-half years, a small mass recurred in the same breast. Operation was repeatedly refused. Four and one-half years after excision the mass had increased slightly, and pain had developed in the pelvis and groins. Small inguinal masses appeared. A letter from the patient's physician stated that she died five years after the mammary tumor was excised, with large inguinal masses and with "generalized carcinomatous metastases" to the pelvis.

Series II: Fifty-seven patients were treated by simple amputation. Of 56 patients who were followed for periods ranging from two to twelve years, 96.4 per cent were followed three years or more, 64.2 per cent five years or more and 17.9 per cent ten years or more.

Two of these patients died, one of carcinoma of the breast and the other of "carcinoma of the stomach." The histories of these 2 cases follow:

Case 23, Group A.—Two years previously a married woman, aged 42, had noted a small mass in the right breast. This had subsided spontaneously. Shortly before her admission to the hospital, a mass had again developed in the lower outer quadrant of the right breast. This was described as being of the size of a hen's egg and freely movable, with none of the clinical signs of malignancy. The breast was amputated and found to contain one large and numerous small cysts varying from microscopic dimensions to diameters of 5 mm. or more. The diagnosis of cystic disease was made by Dr. Bell. Approximately ten years later, generalized deep-seated pain developed. Examination revealed a heretofore undiscovered mass in the remaining breast. Roentgenograms of the skeleton demonstrated diffuse bony metastases. One year later the patient died of generalized carcinomatosis. Unfortunately, none of the slides or tissue blocks from this patient could be obtained for photographic reproduction.

Case 5, Group B.—A married woman, aged 56, had one child, who had not been nursed. One month prior to her admission to the hospital she noticed bleeding from the right nipple. The examining surgeon found a small mass in the lower outer quadrant of the breast. The entire breast was removed, and the diagnosis of cystic disease was made. The patient moved out of the community and was

not seen again by the surgeon. A letter from her husband stated that she died one year later from what her attending physician diagnosed as carcinoma of the stomach.

Recurrences.—Recurrences in the same breast developed in 18 of the patients treated by local excision, new involvement in the opposite breast developed in 15 and both a recurrence and new involvement developed in 2 (table 10). Six of the 18 recurrent growths were treated by local excision and 4 by amputation. No treatment was given 8 patients. Seven of the 15 patients with new involvement underwent local excision; 2 were treated by simple amputation, and 1 by radical amputation under the mistaken clinical diagnosis of cancer. Five received no treatment. One of the 2 patients in whom recurrence and new involvement were combined was untreated; the other underwent simple amputation of the newly involved breast two years later and local excision of the recurrent mass three years later.

TABLE 10.—*Recurrences and New Involvements*

	Local Excision, Series I*						New Involvements, Simple Amputation Series	
	Recurrences			New Involvements				
	L. E.	S. A.	No Treatment	L. E.	S. A.	No Treatment	L. E.	S. A.
Group A.....	5	3	6	5	1	4	1	4
Groups B and C	1	1	..	2	1	1	2	..

* One patient of group A had a radical amputation for a new involvement in the opposite breast. Two patients of group A had both recurrence and new involvement. One received no treatment. On the other local excision was performed for the recurrence and simple amputation of the newly involved breast.

In 7 of the patients treated by simple amputation masses subsequently developed in the remaining breast. Four were treated by simple amputation and 3 by local excision.

A slightly greater tendency to recurrence in the cases of adenocystic disease may be indicated by the finding of recurrences in 21.4 per cent of the combined adenocystic groups (groups B and C), as compared with recurrence in 13.9 per cent of the simple cystic group (group A). However, this difference is too small, and the discrepancy in the number of patients in the two groups too great, to warrant any definite conclusions.

Cystic Disease in Male Patients.—In addition to the cases already described, there were 9 cases of cystic disease in male patients, treated surgically. Their ages varied from 14 to 48 years. Since the epithelial element of the male breast is very limited and consists only of ducts near the nipple, the extent of the pathologic process is always confined to the area of the nipple or its vicinity. The largest lesion was described as being the size of a walnut. Previous masses had been removed in 2 instances. The patients were followed from three to fifteen years. All are living and well. There were no recurrences.

SUMMARY AND COMMENT

Two closely related problems merit discussion. The first is concerned with the diagnostic criteria for the differentiation of benign from malignant hyperplasia. The second is concerned with the probable course of the pathologic process when only the mass or a portion of it is removed and the breast preserved.

Diagnostic Criteria.—The difficulty which confronts a pathologist in the diagnosis of border-line tumors is well illustrated in the following 2 cases:

Mrs. M. R., aged 50, who had borne eleven children was admitted to the Minnesota General Hospital in July, 1926, complaining of a brownish discharge from the right nipple of seven months' duration. Both breasts were pendulous. The right was the larger and demonstrated diffuse nodularity with a definite indurated area above the nipple. Three small axillary lymph nodes were palpable on the same side. At exploration I removed a mass 5 cm. in diameter from the upper half of the breast. The diagnosis of adenocystic disease was made from a frozen section. The operative note describes the breast as the site of "diffuse cystic disease with the major area above the nipple. . . . the gross picture could be easily confused with carcinoma because of the hardness of the tumor." Local excision was performed. Four months later, because of a tumor mass medial to the scar, the patient consulted another surgeon at a private hospital. The recurrent mass was removed, and this time the diagnosis, made by another pathologist, was adenocarcinoma. A radical amputation was performed.

Recently I secured sections of the amputated breast and the axillary lymph nodes. No metastases were found in the nodes. Figure 2 *B* illustrates the section on which the diagnosis of carcinoma was made. Dr. Bell and Dr. O'Brien have reviewed this slide and reaffirm the original diagnosis of adenocystic disease. The patient was alive and well more than six years later.

Mrs. N. H., aged 39, presented herself for operation in February, 1929, for fibroid tumors of the uterus. Five years before a small area of cystic disease had been removed from the left breast, the diagnosis having been made in the department of pathology of the University of Wisconsin. A recurrence of the mass and a new involvement of the opposite breast had been under the observation of her surgeon for two years. Because of increasing induration he had decided to remove the recurrent mass. While the patient was convalescing from a hysterectomy, the mass was removed locally. From frozen sections, Dr. Bell made a diagnosis of adenocystic disease with probable early carcinoma. Simple amputation was performed, and 50 mg. of radium was inserted into the tissues about the wound. A later study of paraffin sections (figs. 2 *C* and *D*) did not eliminate a fear of the possibility that this breast harbored a malignant tumor. Consequently the simple amputation was converted into a radical amputation by the later removal of the axillary glands. The glands showed no evidence of metastases, and the patient is living and well at the time of writing. Dr. Bell has reviewed these sections and is convinced that the lesion is benign and represents only one of the extremely hyperplastic forms of adenocystic disease.

The first of these cases illustrates a difference of opinion between pathologists, while the latter illustrates the natural unwillingness to subject a patient to the risk of an inadequately treated malignant condi-

tion, even though it seems highly probable that the lesion is benign. They are excellent examples of border-line lesions.

Bloodgood (1931) has pointed out that when the diagnosis of malignant growth can be easily made, the course of the disease and its prognosis are characteristic of cancer. When the tumor is of doubtful nature, and the diagnosis is subject to disagreement, the glands are, with the rarest exception, not involved, and the patient survives regardless of the type of treatment.

Slight damage is done to the true picture of either cystic disease or carcinoma if these border-line cases, even though radical amputation is performed, are set apart as a separate group. Their inclusion and acceptance as cases of true malignant changes increase the percentage of cases in which carcinoma is described as arising in an area of cystic disease. Bell estimates the incidence of such occurrence at 3 per cent of all cases of malignant changes, an incidence only slightly higher than the incidence of carcinoma in the normal breast as shown by vital statistics for the year 1929.

Also, by assuming that the lesions represent cancers of low malignancy, one is given a false impression of the curability of cancer. The necessary and commendable conservatism on the part of pathologists restricts the rapid acquisition of knowledge concerning these questionable tumors. Future progress, and the only method by which the field of benign lesions can be enlarged at the expense of the border-line group, lies in the frequent interchange of slides between pathologists and in the publication of photomicrographs of lesions the clinical course of which has already been determined.

Gradually, as confidence grows and as circumstances—such as the refusal of patients to accept, or the inability to withstand, radical operation—add cases of border-line tumors in which limited operations are done, the diagnostic criteria may be shifted in a direction which will increase the benign group and diminish the malignant group.

The diagnostic criteria which have been generally adopted and utilized in the hospitals from which the material here presented was obtained are those of the department of pathology at the University of Minnesota, which teaches that the diagnosis of cystic disease depends largely on the preservation of the lobular arrangement of the breast. Almost any degree of hyperplasia may occur so long as it is confined to lobules. A certain reservation is made in the type of cystic disease producing papillomatous growths in the larger ducts. The difficulty in differentiating this lesion from cancer of the duct has resulted in the recommendation of the complete operation in a number of cases in which it was felt that the lesion was probably benign. Bloodgood (1921) has demonstrated limited invasion of connective tissue in lesions the benign nature

of which he has established by clinical follow-up. Thus far we have been unwilling to overlook invasion as a sign of malignant change.

Figures 3 *A*, 3 *C*, 4 *A* and 4 *C* illustrate lesions which a large proportion of surgical pathologists would call benign, but which some would undoubtedly label as malignant. Attention is called to the greater diagnostic value of low magnifications. Figures 3 *B*, 3 *D*, 4 *B*, 4 *D* and 6 *B* represent photomicrographs of lesions shown with lower magnification in figures 3 *A*, 3 *C*, 4 *A*, 4 *C* and 6 *A*. With a high magnification the differentiation from cancer is difficult or impossible without the knowledge, revealed by low power magnification, that the epithelium is everywhere confined to the ducts or acini.

The picture of cystic disease should not be confused by the presence of hyperplastic forms of the sweat gland type. These structures are frequently encountered in association with all forms of the disease. Figure 1 *C* illustrates a group of acini of the sweat gland type occurring in simple cystic disease. Figure 1 *D* illustrates the same process associated with adenocystic disease. The degree of epithelial activity in these glands is approximately the same, regardless of the activity of the normal-staining epithelium. They are not regarded as precancerous.

Since it is considered that local excision or simple amputation is insufficient to cure true carcinoma, 290 followed cases in which the accuracy of the diagnosis is verified are presented. In none did local cutaneous, axillary or supraclavicular metastases develop, as would be anticipated in the event that a malignant condition had been mistaken for cystic disease.

In 1 patient (case 75, series I, group A) carcinoma developed seven months after the removal of an area of cystic disease. That these represented separate lesions is indicated by the fact that the area of cystic disease was small, of the simple type and located near the nipple, while the malignant growth was of the undifferentiated infiltrating variety, occurring at the edge of the breast near the axilla.

One patient (case 23, series II, group A) who died of generalized metastases eleven years after simple amputation of one breast can logically be considered as having had in the other breast a carcinoma which had gone unrecognized, although the possibility must be entertained that the proper block of tissue from the amputated breast was not received for diagnosis.

In the absence of local cutaneous metastases and of axillary or supraclavicular metastases the death in case 22, series I, group B, cannot be accepted as due to carcinoma of the breast. The presence of inguinal masses and the physician's description of carcinoma in the pelvis suggest that death was due to carcinoma originating in the pelvis.

TABLE 11.—*Series I, Patients Treated by Local Excision (Group A, Simple Cystic Disease)*

Patient	Age	Marital State	Duration of Symptoms	Distribution*	Pain	Discharge	Before Pregnancies	After Pregnancies	Previous Lesions	Follow-Up, Years	Subsequent Involvement	Comment
1	25	M	.....	..	....	..	....	...	.....	7	.....	
2	39	M	.....	L	No	..	Yes	...	.....	6	.....	
3	41	S	2 weeks	L	Yes	..	No	No	.....	6	Same breast, 5 years later	
4	44	M	6 weeks	M	Yes	..	Yes	No	.....	9	.....	
5	55	M	3 months	..	....	..	....	...	.....	4	.....	
6	45	S	10 days	L	No	..	No	No	.....	2	.....	
7	42	M	1 week	L	No	..	Yes	No	.....	7	.....	
8	29	M	3 months	B-M	Yes	..	....	...	.....	3	Same breast, 2 years later	Only one breast operated on; some pain since operation
9	56	M	5 years	L	Yes	B†	Yes	No	.....	3	.....	Some pain since operation
10	..	M	.....	..	....	..	....	...	.....	9	.....	
11	50	S	1 year	L	Yes	S	No	No	.....	5	.....	
12	32	S	4 days	L	No	..	No	No	Opposite breast, local excision 2 years previously	8	.....	
13	41	S	4 weeks	L	No	..	No	No	.....	12	.....	
14	25	S	3 weeks	D	No	..	No	No	.....	12	.....	
15	49	M	.....	L	....	..	Yes	No	.....	7	.....	
16	25	M	6 months	L	....	..	Yes	...	.....	5	.....	
17	39	M	3 weeks	M	....	..	....	...	.....	5	.....	
18	38	M	2½ years	L	No	..	Yes	2	Opposite breast, local excision 6 years previously	4	.....	Had two pregnancies after first operation
19	21	M	4 months	M	No	..	Yes	...	Same breast, abscess at lactation 4 months previously	3	.....	
20	44	S	3 months	B-L	No	..	No	No	.....	5	.....	Bilateral local excision
21	42	M	.....	L	....	..	....	...	Opposite breast, radical amputation 2 years previously for carcinoma	2½	.....	
22	47	M	1 week	L	No	..	Yes	...	.....	3	.....	
23	40	S	2 weeks	L	....	..	No	No	.....	5½	.....	
24	37	S	9 months	..	....	..	No	No	.....	7	.....	
25	50	M	2 weeks	L	No	..	No	No	Opposite breast, local excision 1 year previously	5	.....	Tuberculous glands of same axilla several years previously
26	43	M	.....	L	....	..	No	No	.....	6	.....	
27	46	S	2 weeks	..	....	..	No	No	.....	12	.....	
28	40	M	.....	..	....	..	....	...	.....	10	.....	Died 10 years later; "paralytic stroke"
29	28	M	.....	M	....	..	Yes	...	.....	3	.....	
30	36	M	3 days	L	No	..	Yes	...	.....	3	.....	
31	38	M	1 week	L	No	..	No	No	.....	3	.....	
32	47	M	4 months	L	No	..	Yes	...	Opposite breast, local excision 4 years previously	3	.....	
33	32	M	6 months	L	Yes	..	....	...	.....	8	.....	
34	42	S	1 month	L	No	..	No	No	Opposite breast, local excision 4 years previously	8	.....	
35	37	S	4 months	L	No	..	No	No	.....	6	.....	
36	38	M	.....	L	No	..	Yes	...	.....	5	.....	
37	..	S	.....	..	....	..	No	No	.....	4	.....	
38	50	M	.....	L	....	..	....	...	.....	4	.....	
39	45	M	6 weeks	..	No	..	No	No	.....	4	.....	
40		M	3 months	D	No	..	....	...	Opposite breast, local excision 8 years previously	10	.....	

36	38	M	4 months	L	No	..	No	No	.....	6	.....	
37	..	S	.....	L	No	..	Yes	...	.....	5	.....	
38	50	M	.....	..	....	..	No	No	.....	4	.....	
				L	....	..	....	...	.....	4	.....	
39	45	M	6 weeks	..	No	..	No	No	.....	4	.....	
40	..	M	3 months	D	No	..	....	...	Opposite breast, local excision 3 years previously	10	.....	
41	40	M	4 days	L	Yes	..	Yes	...	Same breast, abscess at lactation 10 years previously	2	.....	
42	23	S	1 year	L	No	..	No	...	.....	6	.....	
43	47	M	2½ years	L	Yes	..	Yes	No	.....	9	.....	
44	38	M	4 days	L	No	..	Yes	...	.....	3	.....	
45	34	S	1 week	..	No	..	No	No	.....	6	Opposite breast, local excision 1 year later	
46	42	M	.....	..	No	..	....	...	.....	9	.....	
47	46	M	.....	..	....	..	....	...	.....	10	.....	
48	49	M	.....	L	No	..	Yes	No	Same breast, local excision 6 years previously	9	.....	
49	48	M	10 days	L	No	..	Yes	No	.....	2	.....	
50	37	M	.....	L	No	..	....	No	.....	12	.....	
51	50	S	1 day	L	No	..	No	No	.....	9	.....	
52	45	M	.....	L	....	..	....	...	.....	14	.....	
53	49	M	.....	L	Yes	..	Yes	...	Opposite breast, local excision 1 year previously	3	.....	
54	50	S	.....	L	No	..	No	No	.....	10	.....	
55	41	M	1 day	L	No	..	No	No	.....	8	.....	
56	22	M	8 months	L	Yes	..	Yes	No	.....	6	Opposite breast, mass 6 years later	Some pain since operation
57	35	S	2 months	..	Yes	..	No	No	.....	3	Same breast, simple amputation 3 years later	
58	37	M	1 month	..	No	..	....	...	.....	10	Opposite breast, local excision 4 years later	
59	40	M	.....	L	....	..	....	...	.....	9	.....	
60	34	S	2 months	L	....	..	No	No	.....	7	.....	
61	36	M	.....	L	Yes	..	....	...	.....	6	.....	
62	41	S	.....	L	No	..	No	No	.....	11	Opposite breast, simple amputation 2 years later; same breast, local excision 3 years later	
63	25	S	.....	L	No	..	No	...	.....	4	.....	
64	53	M	1 week	L	No	..	....	No	.....	2	.....	
65	28	M	2 months	L	Yes	..	No	...	.....	2	.....	
66	26	S	2 months	M	Yes	..	No	...	.....	3	Opposite breast, mass 3 years later	
67	40	S	1 week	L	No	..	No	No	.....	11	.....	
68	35	M	15 years	L	Yes	..	Yes	Yes	.....	13	.....	
69	45	S	1 month	L	Yes	..	No	No	.....	4	.....	
70	46	S	5 months	L	No	..	No	No	.....	8	Same breast, recurrence; opposite breast, new mass 7 years later	
71	22	M	1 year	..	....	..	Yes	...	.....	8	.....	
72	40	M	3½ months	..	No	..	....	...	.....	9	Opposite breast, simple amputation 7 year later	
73	34	M	4 months	L	No	..	Yes	No	.....	6	.....	
74	38	M	20 years	..	No	..	Yes	...	.....	13	.....	
75	45	M	.....	L	Yes	..	No	No	Same breast, local excision 4 years previously	..	Same breast, local excision 7 months later; diagnosis, carcinoma; radical amputation the next month	
76	50	M	2 weeks	L	No	..	....	No	.....	2	.....	
77	31	M	.....	L	No	..	Yes	...	.....	3	.....	

TABLE 11.—*Series I, Patients Treated by Local Excision (Group A, Simple Cystic Disease)—Continued*

Patient	Age	Marital State	Duration of Symptoms	Distribution*	Pain	Discharge	Before Pregnancies	After Pregnancies	Previous Lesions	Follow-Up, Years	Subsequent Involvement	Comment
78	36	S	2 years	L	No	..	No	No	Opposite breast, local excision 8 years previously	4	.....	
79	27	M	2 years	L	Yes	..	Yes	...	.....	6	.....	
80	46	M	5 days	L	No	..	Yes	No	.....	4½	Same breast over 1 year later, 3 subsequent local excisions, final one removing remainder of breast tissue	
81	20	S	2 months	L	No	..	No	...	.....	3	.....	
82	33	M	7 years	L	No	..	....	...	.....	5	.....	
83	62	M	1 year	B-L	No	..	Yes	No	.....	2	Bilateral simple amputation 2 years later	Bilateral local excision
84	42	M	1 year	L	Yes	..	....	...	Opposite breast, radical amputation 1 year previously for carcinoma with axillary metastases	7	.....	
85	39	M	2 months	B-L	No	..	Yes	...	.....	14	.....	Bilateral local excision
86	40	M	3 months	..	....	..	....	...	.....	6	.....	
87	36	S	2 months	B-L	No	..	No	No	.....	5	One breast, recurrence	Bilateral local excision
88	49	M	.....	..	....	..	....	...	.....	11	.....	
89	25	M	1 year	B-L	No	..	Yes	...	.....	2	.....	Only one breast operated on
90	42	M	1 week	L	No	..	No	No	.....	9	.....	
91	37	S	3 weeks	L	No	..	No	No	.....	2	.....	
92	41	S	5 months	L	No	..	No	No	.....	2	Same breast, recurrence	
93	29	M	1 week	L	No	..	Yes	...	.....	3	.....	
94	36	M	.....	..	....	..	....	...	.....	5	.....	
95	30	M	6 days	L	Yes	..	....	...	.....	4	.....	
96	42	M	.....	B-L	No	..	....	...	One breast, local excision 14 years previously	4	Opposite breast, local excision 3 years later	Bilateral local excision
97	62	M	3 months	..	Yes	..	....	...	.....	2	.....	Some pain since operation
98	..	M	.....	..	....	..	....	...	.....	10	.....	
99	48	S	.....	B-L	Yes	..	No	No	.....	5	.....	Only one breast operated on
100	42	M	2 months	L	....	..	....	....	.....	5	.....	
101	32	M	3 months	L	No	..	No	No	.....	14	.....	
102	..	S	.....	..	....	..	....	...	.....	3	.....	
103	32	M	3 months	L	....	..	....	...	.....	3	Same breast, recurrence 2 years later	
104	47	M	.....	L	No	..	....	...	.....	3	Opposite breast, mass 2 years later	
105	38	M	5 days	L	No	..	Yes	...	.....	9	.....	
106	38	M	4 months	L	Yes	..	....	...	.....	11	.....	
107	23	S	2 months	L	No	..	No	...	.....	3	.....	
108	43	S	2 weeks	L	No	..	No	No	.....	5	.....	
109	25	M	.....	..	....	..	....	Yes	.....	13	.....	
110	43	M	2 weeks	L	No	..	Yes	No	.....	3	.....	
111	34	S	3 days	L	No	..	No	No	.....	11	Opposite breast, local excision 11 years later	
112	40	M	3 months	L	No	..	No	No	Opposite breast, local excision 2 years previously	2	.....	
113	30	M	3 months	L	Yes	..	....	...	.....	3	.....	
114	21	M	3 months	L	Yes	..	....	...	.....	3	Opposite breast, mass 3 years later	
115	24	M	3 months	..	No	..	Yes	...	.....	2	.....	In the three subsequent preg-

111	34	S	3 days	L	No	..	No	No	.....	3	.....	
112	40	M	3 months	L	No	..	No	No	Opposite breast, local excision 2 years previously	11	Opposite breast, local excision 11 years later	
113	30	M	3 months	L	Yes	..	....	...	.....	2	.....	
114	21	M	3 months	L	Yes	..	....	...	.....	2	.....	
115	34	M	3 months	..	No	..	Yes	...	.....	3	Opposite breast, mass 3 years later	
116	40	M	7 years	L	No	..	Yes	3	.....	2	.....	
117	30	M	1 week	L	No	..	No	...	.....	6	.....	In the three subsequent pregnancies breast did not lactate
118	42	M	.....	..	....	..	....	...	.....	4	.....	
119	30	M	2 months	..	....	..	....	...	.....	7	.....	
120	40	S	6 days	L	No	..	No	No	.....	7	Same breast, local excision 2 months later	Some pain since operation
121	32	M	.....	L	No	..	Yes	...	.....	10	Opposite breast, local excision 2 years later	
122	26	M	2 weeks	..	No	..	Yes	...	.....	5	.....	
123	24	S	.....	L	....	..	No	...	.....	12	.....	
124	40	M	.....	L	....	..	....	...	.....	3	.....	
125	33	M	.....	..	....	..	....	...	.....	3	.....	
126	51	M	3 days	L	No	..	Yes	...	.....	4	.....	
127	31	M	2 years	L	Yes	..	Yes	...	.....	6	.....	
128	51	M	15 years	L	Yes	..	....	No	.....	5	.....	
129	38	M	5 years	L	Yes	8	Yes	No	Same breast, abscess at lactation 5 years previously	12	.....	
130	50	M	.....	L	....	..	....	...	.....	8	.....	
131	42	M	3 months	L	Yes	..	No	No	.....	4	.....	
132	29	M	3 months	L	No	..	....	...	.....	6	.....	
133	45	M	3 months	L	No	..	Yes	...	.....	6	.....	
134	56	S	10 days	L	Yes	..	No	No	.....	6	.....	
135	37	M	.....	..	....	..	Yes	...	.....	3	.....	Menopause at 19 years; injury to spine
136	43	M	1 day	L	No	..	No	No	.....	2	.....	
137	48	M	6 months	L	No	..	Yes	No	.....	6	.....	
138	52	M	2 days	L	No	..	Yes	No	.....	8	.....	
139	45	M	1 week	L	No	..	....	No	.....	9	.....	
140	35	M	.....	B-L	....	..	Yes	...	.....	7	.....	
141	43	M	3 years	L	....	B	....	...	.....	7	.....	Only one breast operated on; enlarged gland in axilla
142	62	M	4 months	L	Yes	..	....	No	.....	3	.....	
143	28	M	2 years	L	....	..	....	...	.....	14	.....	Some pain since operation
144	35	M	4 months	..	No	..	....	...	Same breast, infection 2 years previously at lactation	7	.....	
145	46	M	2 years	L	No	..	Yes	No	.....	6	.....	
146	34	M	10 months	L	Yes	..	Yes	1	.....	5	.....	
147	47	M	1 month	L	Yes	..	....	...	.....	10	.....	
148	22	S	.....	..	....	..	....	1	.....	12	.....	
149	24	S	3 years	..	No	..	No	No	.....	4	.....	Married since; nursed child
150	33	M	1 day	L	No	..	Yes	...	.....	7	Same breast, local excision 2 years later; same breast, recurrence	Some pain since operation
151	21	S	6 weeks	L	Yes	..	....	...	.....	8	.....	
152	..	S	.....	..	....	..	....	...	.....	7	.....	Tuberculous glands of axilla removed at same time
153	44	M	6 weeks	L	No	..	Yes	No	.....	9	.....	
154	40	M	2 months	L	No	..	Yes	...	.....	11	.....	
155	35	S	1 week	L	No	..	No	No	.....	5	.....	
156	23	S	1 week	L	Yes	..	No	...	.....	5	.....	
157	43	M	2 weeks	L	Yes	..	Yes	...	.....	4	.....	
158	52	S	2 weeks	..	No	..	No	No	Same breast, local excision 2 years previously	3	.....	
										5	.....	

TABLE 11.—*Series I, Patients Treated by Local Excision (Group A, Simple Cystic Disease)—Continued*

Patient	Age	Marital State	Duration of Symptoms	Distribution*	Pain	Discharge	Before Pregnancies	After Pregnancies	Previous Lesions	Follow-Up, Years	Subsequent Involvement	Comment
159	34	S	6 weeks	L	No	..	No	No	Opposite breast, local excision 2 years previously	7	.....	
160	48	M	2 days	L	No	..	No	No	.....	9	.....	
161	42	M	1 week	L	No	..	Yes	...	.....	3	Opposite breast, local excision 1 year later	
162	37	M	2 days	L	No	..	Yes	...	.....	4	.....	
163	40	S	2 weeks	L	No	..	No	No	.....	5	.....	
164	44	M	3 weeks	L	No	..	Yes	...	.....	4	.....	
165	35	M	.....	..	....	..	Yes	No	.....	3	.....	
166	44	M	1 month	L	No	..	No	No	Opposite breast, local excision 1 year previously	4	Same breast, local excision 3 years later	
167	30	S	7 months	M	Yes	..	No	No	.....	2	.....	Some pain since operation
168	22	S	3 years	..	No	..	No	...	Same breast, local excision 4 years previously	5	.....	
169	40	M	8 months	L	Yes	..	Yes	...	.....	5	.....	
170	46	M	2 months	L	No	..	No	No	.....	7	.....	
171	47	S	6 years	B-M	Yes	..	No	No	.....	5	.....	Only one breast operated on
172	24	S	.....	M	No	..	No	...	.....	4	.....	
173	..	M	1 month	L	No	..	....	...	.....	10	.....	
174	44	M	6 weeks	L	No	..	Yes	No	.....	7	.....	
175	36	M	3 weeks	L	No	..	....	...	.....	6	.....	
176	48	S	3 years	L	Yes	..	No	No	Opposite breast, simple amputation 7 years previously	10	.....	
177	29	M	.....	M	No	..	No	3	.....	7	.....	
178	46	M	.....	B-L	No	..	Yes	No	.....	3	.....	Bilateral local excision
179	..	M	.....	..	....	..	....	...	.....	5	.....	Five years later committed suicide; insane
180	41	S	3 months	L	Yes	..	No	No	.....	10	.....	
181	37	M	3 years	L	No	..	No	No	.....	4	.....	
182	48	M	6 weeks	L	Yes	..	Yes	No	.....	9	.....	
183	42	M	4 months	L	Yes	..	....	...	Same breast, local excision 16 months previously; opposite breast, simple amputation 3 years previously	2	.....	
184	28	M	5 days	B-M	Yes	..	Yes	Yes	.....	5	.....	Only one breast operated on
185	37	S	.....	..	....	..	No	No	.....	3	.....	
186	39	S	.....	L	No	..	No	No	.....	7	.....	
187	51	M	1 month	L	Yes	..	Yes	No	.....	2	Same breast, recurrence 1½ years later	
188	43	S	6 weeks	L	No	..	No	No	.....	4	.....	
189	33	M	1 year	L	....	..	Yes	2	.....	6	.....	
190	34	M	6 months	L	....	..	....	...	.....	6	.....	Some pain since operation
191	54	M	.....	B	....	..	....	...	.....	2	.....	Left breast, local excision, simple cystic disease; right breast, simple amputation, cystic disease and adenoma

* L denotes local, M multiple, B bilateral and D diffuse involvement.
† Bloody.

After a consideration of the literature, it seems obvious that the criteria here used represent entirely different standards for the diagnosis of malignant tumors from those used by many writers.

That pathologists are revising their diagnostic criteria is shown by Bloodgood who in 1915 and again in 1930 submitted sections of borderline tumors to able and prominent pathologists. Whereas in 1915 the majority of sections had been considered malignant, in 1930 most pathologists considered them benign.

It may reasonably be concluded that in this series of 290 cases, the diagnosis of benign lesions has been substantiated by the clinical course of the disease and that the diagnostic criteria as established at the University of Minnesota have thus far proved safe.

Probable Course of the Disease.—In drawing conclusions relative to the risk of malignant change occurring in cystic disease, we are justified in using cases in which only the clinically recognizable or grossly pathologic areas have been removed. The tendency of the process to extend and to involve the opposite breast is generally recognized (Reclus [1883], Schimmelbusch, Lichtenhahn, Cheatle [1930], and others). The high incidence of recurrence is consistent with this tendency. Furthermore, the pathologic process is always more extensive than the clinical or gross pathologic observations indicate (Brissaud [1888], Saar, and others). Tietze (1904) and Goens-Rosales found a high incidence of cystic changes in elderly women without clinical evidence of the disease, while Askanazy (1925) found a similar high incidence, not only in senile breasts, but in the breasts of women under 40. It is probable that local excision of clinically recognizable lesions never effects a cure in patients with cystic disease.

The recognized tendency toward bilateral involvement renders the 57 cases in which simple amputation was performed of some value, but the greatest dependence in determining the risk of subsequent malignant change must be placed on series in which the breasts have been preserved. Of 233 cases of this type carcinoma of the breast developed in only 1. For reasons previously outlined, this development is reasonably considered coincidental with rather than an outgrowth of the previous disease process.

Of the 233 patients, 43, or 18 per cent, had lesions composed of forms in which epithelial hyperplasia was active or in which it dominated the picture. In none of these breasts did carcinoma subsequently develop. There is no evidence to support the view held by Semb, Kilgore (1928) and others that this form, in contrast to simple cystic disease, is susceptible to malignant change.

Aside from showing the suggested greater tendency of hyperplastic forms to recur and to involve the opposite breast, nothing was learned and no advantage was gained by separating and grading adenocystic

Left breast, local excision, simple cystic disease; right breast, simple amputation, cystic disease and adenoma

* L denotes local, M multiple, B bilateral and D diffuse involvement.
† Biopsy.

TABLE 12.—*Series I, Patients Treated by Local Excisions (Group B, Adenocystic Disease, Grade I)*

Patient	Age	Marital State	Duration of Symptoms	Distribution	Pain	Discharge	Before Pregnancies	After Pregnancies	Previous Lesions	Follow-Up, Years	Subsequent Involvement	Comment
1	22	M	1 year	L*	Yes	..	....	...	.....	5	.....	
2	36	M	16 years	L	No	..	Yes	No	.....	7	.....	
3	40	M	2 days	L	Yes	..	Yes	...	.....	2½	Opposite breast, local excision 18 months later	
4	47	S	3 weeks	L	No	..	No	No	.....	11	Opposite breast, radical amputation 2 years later; no carcinoma	
5	46	M	3 weeks	L	No	..	....	No	.....	3	.....	
6	33	S	3 months	L	No	..	No	No	.....	6	.....	
7	45	M	1 week	L	Yes	..	Yes	...	.....	9	.....	
8	34	M	3 months	L	No	..	....	...	.....	6	.....	
9	38	M	2 weeks	L	Yes	..	Yes	...	.....	7	.....	
10	24	M	.....	L	No	..	....	3	.....	12	.....	Axillary mammary gland enlarged with each pregnancy
11	43	S	1½ years	L	No	..	No	No	.....	7½	Opposite breast, local excision 4 years later	Some pain since operation
12	22	S	3 months	...	No	..	No	No	.....	12	.....	Died 12 years later; "heart and kidney trouble"
13	29	M	.....	..	No	..	Yes	No	.....	3	.....	
14	..	M	.....	..	....	..	Yes	...	.....	3	.....	
15	39	M	10 years	L	Yes	..	....	...	.....	2	.....	Some pain since operation
16	50	M	.....	L	....	..	....	...	.....	4	.....	
17	50	M	1 week	L	No	..	Yes	No	.....	3	.....	Some pain since operation
18	43	M	4 months	..	No	B†	....	...	Opposite breast, local excision 4 months previously	8	Opposite breast, simple amputation 2 years later	Some pain since operation
19	39	M	3 weeks	L	Yes	..	7	...	.....	5	.....	
20	23	M	3 months	L	Yes	..	Yes	...	.....	3	.....	
21	38	M	1 year	L	Yes	..	No	No	.....	3	.....	
22	37	S	.....	..	....	..	....	...	.....	5	Same breast, recurrence 2 years later	Died 5 years later; pelvic metastases
23	41	S	.....	..	No	..	No	No	.....	3	.....	
24	46	M	.....	L	....	..	....	...	.....	5	Opposite breast, mass 4 years later	
25	..	S	.....	L	No	..	No	No	.....	3	.....	
26	..	M	.....	L	No	..	....	...	.....	6	.....	
27	50	M	3 weeks	L	No	..	Yes	No	.....	8	.....	
28	65	M	1 day	L	No	..	Yes	No	.....	6	.....	
29	47	M	.....	L	No	..	Yes	No	.....	10	Same breast, local excision 5 and 10 years later	

* Local involvement.
† Bloody.

* Local involvement.
† Bloody.

TABLE 13.—*Series I, Patients Treated by Local Excision (Group C, Adenocystic Disease, Grade II)*

Patient	Age	Marital State	Duration of Symptoms	Distribution*	Pain	Discharge	Before Pregnancies	After Pregnancies	Previous Lesions	Follow-Up, Years	Subsequent Involvement	Comment
1	22	S	.....	L	No	..	No	...	.....	3	.....	
2	34	M	5 days	L	No	..	No	No	.....	10	.....	
3	23	S	2 years	B-L	No	..	No	Yes	.....	12	.....	Only one breast operated on
4	29	S	2 years	..	Yes	..	No	...	.....	3	Same breast, recurrence	Some pain since operation
5	65	M	6 months	L	No	..	....	No	.....	5	.....	
6	38	S	10 years	M	Yes	..	No	No	.....	4	.....	
7	42	M	.....	L	....	..	....	...	.....	3	.....	
8	43	M	2 years	B-L	No	..	....	...	.....	3	.....	Bilateral local excision
9	35	S	1 week	L	Yes	..	....	...	.....	2	Same breast, simple amputation 2 years later	
10	21	S	3 months	..	....	..	No	2	.....	3	.....	
11	36	S	3 years	L	No	..	No	No	.....	5	.....	
12	21	S	1 month	L	No	..	No	...	.....	2	.....	
13	27	M	2½ years	..	No	..	....	...	.....	2	.....	

* L indicates local, B bilateral and M multiple involvement.

TABLE 14.—*Series II, Patients Treated by Simple Amputation (Group A, Simple Cystic Disease)*

Patient	Age	Marital State	Duration of Symptoms	Distribution*	Pain	Discharge	Before Pregnancies	After Pregnancies	Previous Lesions	Follow-Up, Years	Subsequent Involvement	Comment
1	45	S	3 days	D	No	..	No	No	.....	12	.....	
2	46	M	Several months	L	....	..	....	...	.....	5	.....	
3	25	M	1 month	L	Yes	..	Yes	...	.....	5	.....	
4	37	S	3 weeks	..	Yes	..	No	No	.....	3	Opposite breast, local excision 2 years later	
5	41	M	.....	B-M	....	..	Yes	...	Both breasts, local excision 5 years previously	8	.....	Bilateral simple amputation
6	38	S	.....	L	....	..	No	No	.....	6	.....	
7	39	M	2 weeks	L	No	..	No	No	.....	6	.....	
8	34	M	6 months	D	No	..	....	...	.....	7	.....	
9	36	M	2 weeks	M	No	..	Yes	No	Same breast, mastitis 16 years previously	3	.....	
10	31	M	6 years	L	No	..	Yes	...	.....	4	.....	
11	39	S	9 years	..	Yes	B†	No	No	Same breast, local excision 9 years previously	4	.....	
12	46	M	4 days	L	No	..	....	...	.....	3	.....	
13	40	M	2 months	L	....	..	10	1	Same breast, abscess previously	8	.....	
14	29	M	1 year	L	No	..	Yes	No	.....	9	.....	
15	44	M	.....	M	No	..	Yes	No	.....	8	Opposite breast, simple amputation 4 months later	
16	38	M	2 months	..	No	..	Yes	No	Opposite breast, radical amputation 6 months previously; adenocarcinoma	9	.....	
17	43	M	6 months	L	Yes	..	Yes	...	.....	3	.....	
18	44	M	2 years	D	No	..	....	...	Opposite breast, radical amputation 2 years previously	6	.....	
19	..	M	2 months	..	....	..	Yes	...	.....	9	.....	
20	45	S	5 days	M	No	..	No	No	.....	3	.....	

21	38	M	.....	..	....	..	....	...	.....	10	.....	
22	47	S	1 week	..	No	..	No	No	Same breast, local excision twice 2 years previously	11	.....	
23	42	M	2 years	..	No	..	....	...	.....	11	.....	Died 11 years later; metastases to bone
24	33	M	5 months	D	Yes	..	....	...	.....	3	.....	
25	39	M	.....	L	No	..	Yes	...	Same breast, local excision 2 years previously	3	.....	
26	48	S	3 weeks	L	No	..	No	No	Same breast, local excision 6 years previously; opposite breast, simple amputation	10	.....	
27	46	S	3 months	M	Yes	..	No	No	Opposite breast, simple amputation 2 years previously	11	.....	
28	46	S	3 months	L	....	..	No	No	.....	5	.....	
29	..	M	2 weeks	L	Yes	..	Yes	...	.....	9	.....	
30	34	M	12 years	D	....	..	Yes	...	.....	2	.....	
31	45	M	4 days	L	Yes	..	Yes	No	.....	7	.....	
32	40	M	3 years	..	....	..	....	...	Opposite breast, simple amputation several years previously	6	.....	
33	52	M	6 weeks	M	No	..	Yes	No	Opposite breast, simple amputation 4 months previously	8	.....	
34	39	S	.....	M	....	..	No	No	.....	4	.....	
35	37	S	.....	..	No	..	No	No	Opposite breast, simple amputation 1 year previously	12	.....	
36	46	M	3 months	L	No	..	....	...	.....	5	Opposite breast, simple amputation 2 months later	
37	54	M	3 months	..	Yes	..	....	No	.....	9	.....	
38	41	M	1 year	..	....	..	....	...	Same breast, local excision 4 months previously	3	Opposite breast, simple amputation 2 years later	
39	45	M	.....	L	....	..	....	...	Opposite breast, simple amputation 1 year previously	7	.....	
40	34	S	10 days	L	No	..	No	No	.....	4	Opposite breast, simple amputation 6 months later	
41	37	M	1 year	L	No	..	No	No	.....	6	.....	
42	49	M	6 months	M	No	..	Yes	No	.....	5	.....	Before operation 4 series of high voltage roentgen treatments had been given with no benefit

* D denotes diffuse, L local, B bilateral, and M multiple involvement.
† Bloody.

TABLE 15.—*Series II, Patients Treated by Simple Amputation (Group B, Adenocystic Disease, Grade I)*

Patient	Age	Marital State	Duration of Symptoms	Distribution*	Pain	Discharge	Before Pregnancies	After Pregnancies	Previous Lesions	Follow-Up, Years	Subsequent Involvement	Comment
1	39	M	6 months	M	No	..	No	No	.....	3	.....	
2	40	M	3 weeks	D	Yes	..	....	...	.....	3	.....	
3	31	M	6 months	L	Yes	..	Yes	Yes	Same breast, abscess 10 years previously	11	.....	
4	50	M	6 months	D	No	..	No	No	.....	10	.....	
5	56	M	1 month	..	No	B†	Yes	No	.....	..	Died 1 year later; carcinoma of stomach	
6	47	S	.....	L	....	..	No	No	.....	4	.....	
7	56	S	4 days	D	No	..	No	No	Same breast, local excision 6 weeks previously	4	.....	
8	38	M	2 years	M	No	..	....	...	.....	2	.....	

* M denotes multiple, D diffuse and L local involvement.
† Bloody.

TABLE 16.—*Series II, Patients Treated by Simple Amputation (Group C, Adenocystic Disease, Grade II)*

Patient	Age	Marital State	Duration of Symptoms	Distribution*	Pain	Discharge	Before Pregnancies	After Pregnancies	Previous Lesions	Follow-Up, Years	Subsequent Involvement	Comment
1	45	M	1 year	D	Yes	B†	....	...	.....	4	Opposite breast, local excision 3½ years later	
2	57	M	3 years	L	No	B	Yes	No	.....	4	.....	
3	32	M	.....	..	....	..	Yes	...	.....	4	.....	
4	48	M	3 months	L	No	..	Yes	No	.....	5	.....	
5	29	S	.....	..	....	B	No	No	.....	7	Opposite breast, local excision 6 years later	
6	36	S	2 years	M	Yes	..	No	No	Opposite breast, simple amputation 2 years previously	11	.....	
7	49	M	9 months	..	....	..	....	No	.....	5	.....	Some pain since operation

* D denotes diffuse, L local and M multiple involvement.
† Bloody.

disease. Of the 57 patients treated by amputation, carcinoma probably developed in the opposite breast of 1 patient, making a total incidence of 2 cases of carcinoma of the breast in 290 of the patients who were followed, or 0.7 per cent.

CONCLUSIONS AND RECOMMENDATIONS

The evidence here advanced justifies the following conclusions:

Cystic disease is not a precancerous lesion, and malignant changes are no more likely to develop in a breast showing the disease than in one which is entirely normal. No evidence was obtained from this material to justify the contention that the adenocystic form of the disease is more dangerous than the simple cystic form.

Diagnostic criteria which have withstood the clinical test of time are available and justify a more liberal interpretation of the histologic picture in favor of benignancy.

The adaptation of these views to the treatment of cystic disease will still allow considerable latitude in the procedures recommended.

One may approach the problem of treatment with the easy philosophy that the total removal of mammary tissue will for all time relieve the patient of worry and risk, and the surgeon of responsibility. However, it is assumed as basic that the preservation of the breasts, both from the functional and the cosmetic standpoint, is desirable and commendable if it can be accomplished with reasonable safety to the patient.

From the standpoint of risk of malignant degeneration, there is no more justification for the amputation of breasts containing cystic disease than for the routine removal of normal breasts to prevent the inevitable occurrence of carcinoma in approximately 2 per cent of cases.

Using the word "conservative" in its broadest meaning and endowing it with all surgical virtue, I have formulated the following policy as representing the conservative attitude toward cystic disease of the breast. It is based on the fear that carcinoma may be present and unsuspected at the time of examination, rather than on the fear that a malignant condition will subsequently develop. It calls for an exploratory incision and limited operations frequently and only rarely for amputations. It throws a great burden on the pathologist and demands his thorough familiarity with the various forms of cystic disease which may simulate malignancy. It is designed to afford the patient the maximum protection with the minimum anatomic and functional loss.

All single solid tumors in a woman over 25 years of age should be removed for diagnosis. While, as Ewing has stated, the diagnosis of carcinoma can, in the majority of cases, be made from the gross tissue at the operating table, a competent pathologist with facilities for examining frozen sections should be available for the 10 or 20 per cent of cases in which this is not possible.

Single small localized areas, even though clinically characteristic of cystic disease, are better examined by a biopsy. Under the age of 25 malignant tumors are so rare that in the absence of clinical signs of malignancy there is no need for operation, or at least operation may be delayed.

While the presence of multiple tumors in one or both breasts is strong evidence of the benign nature of a process, I prefer to remove one or more of the most suspicious on the basis that if carcinoma is developing in a breast containing benign masses, it can only be recognized clinically after it has become characteristic and hence after late signs of malignancy have developed. By excising the most suspicious area the danger is not obviated, but it is minimized.

Cysts sufficiently large to be recognized clinically or by transillumination also strongly indicate benignancy. The incidence of 5 carcinomas in 500 cases of blue-domed cysts was reported by Bloodgood (1929). In each case it was the malignant tumor which was palpated and operated on. The cysts were only accidentally discovered at operation.

There is a sufficiently large number of reported cases, however, in which cancer developed in the wall or in the immediate neighborhood of a cyst (Bartlett [1924], Adams, McGlannan, Fitzwilliams and others) to make the excision of a single cyst advisable. When cysts are multiple, the risk involved does not warrant an extensive procedure or the loss of the breast.

There is an increasingly large number of patients with a condition so characteristic that no operation is recommended. The best example of this is the diffuse form of cystic disease, the shotty or nodular breast, the greater part of one or both breasts being involved and no one area standing out more definitely than another. Such patients need not be operated on, but must be closely observed.

When one area in a diffuse process stands out more prominently or when, under observation, an area develops and becomes more prominent, exploratory incision and biopsy are indicated. The remainder of the breast is of no value in determining the nature of this newly developing portion.

Bleeding from the nipple demands the localization of the source of the blood and the removal of that portion of the breast for diagnosis. Over 50 per cent of such cases will prove benign. When the sources are multiple, it may be necessary to remove the breast. This course is dictated not through fear that malignant changes will develop, but rather because they are already established and responsible for a part of the bleeding. The radical operation should be performed only when malignancy is proved.

In applying these principles the age of the patient must be given some consideration. What is a conservative procedure in a woman of 30 is not necessarily so in one of 50. In the older woman the period

of function is past, the loss of the breast is not of such vital concern, and the risk of developing cancer is greater.

For this reason I believe that in certain instances simple amputation of the breast is justified. Particularly is this true when limited excision does not remove the entire process, and when the consistency of the remaining mammary tissue so obscures a developing carcinoma that the patient would lose her greatest opportunity for an early diagnosis and cure.

There can be no compromise with the dictum which demands radical operation in all cases in which histologic examination still leaves the experienced pathologist in doubt.

Greater knowledge and altered diagnostic criteria will in the future cause fewer unnecessary radical amputations to be performed.

In view of the limitations imposed on clinical methods of diagnosis, the procedures outlined seem reasonable and are consistent with my conception of what is best for the patient.

BIBLIOGRAPHY

Abbe, R.: Consideration of Mammary Cysts in the Differentiation of Breast Tumors, M. Rec. **64**:241, 1903.

Adair, F. E.: Sanguineous Discharge from the Nipple and Its Significance in Relation to Cancer of the Breast, Ann. Surg. **91**:197, 1930.

Adams, L. J.: Carcinoma in a Blue-Domed Cyst of the Breast, Canad. M. A. J. **19**:190, 1928.

Askanazy, M.: Die Cysten-Mamma und ihr latenter Zustand, Schweiz. med. Wchnschr. **55**:1017, 1925.

Die Beziehungen der gutartigen Erkrankungen der Brustdrüse zum Mammakarzinom, Beitr. z. path. Anat. u. z. allg. Path. **87**:396, 1931.

Bartlett, E. I.: Clinically Doubtful Breast Tumors: Their Diagnosis and Treatment, Ann. Surg. **73**:740, 1921.

Breast Hypertrophy; Nonsurgical Breast Conditions, Surg., Gynec. & Obst. **38**:798, 1924.

The Treatment of Blue Dome Cyst, J. A. M. A. **83**:343 (Aug. 2) 1924.

Bell, E. T.: Personal communication to the author.

Berka, F.: Die Brustdrüse verschiedener Altersstufen und während der Schwangerschaft, Frankfurt. Ztschr. f. Path. **8**:203, 1911.

Bertels, A.: Ueber die Mastitis chronica (cystica) und ihren Uebergang in Carcinom, Deutsche Ztschr. f. Chir. **124**:9, 1913.

Billroth, T.: Die Krankheiten der Brustdrüsen, Deutsche Chirurgie, pt. 41, Stuttgart, Ferdinand Enke, 1880.

Birkett, J.: Clinical Lecture on the Simple Cyst Containing Serous Fluid Developed in the Mammary Gland, Lancet **2**:105, 1868.

On Some of the New Growths Developed in the Breast Associated with Cysts, Guy's Hosp. Rep. **18**:413, 1873.

Bloodgood, J. C., in discussion on Stewart, J. C.: J. A. M. A. **43**:367 (Aug. 6) 1904.

Senile Parenchymatous Hypertrophy of the Female Breast, Surg., Gynec. & Obst. **3**:721, 1906.

The Pathology of Chronic Cystic Mastitis of the Female Breast, with Special Consideration of the Blue-Domed Cyst, Arch. Surg. **3**:445 (Nov.) 1921.

Benign Lesions of the Female Breast for Which Operation is not Indicated, J. A. M.A. **78**:859 (March 25) 1922.

Benign Tumors of the Breast, Encapsulated Adenoma, Ann. Surg. **79**:172, 1924.

Chronic Cystic Mastitis of the Diffuse, Nonencapsulated, Cystic Adenomatous Type, ibid. **90**:886, 1929.

The Blue-Domed Cyst in Chronic Cystic Mastitis, J. A. M. A. **93**:1056 (Oct. 5) 1929.

Border Line Breast Tumors, Ann. Surg. **93**:235, 1931.

Borchardt, M., and Jaffé, R.: Zur Kenntnis der Zystenmamma, Beitr. z. klin. Chir. **155**:481, 1932.

Brissaud, M.: Anatomies pathologique de la maladie kystique des mamelles, Arch. de physiol. norm. et path. **3**:98, 1883.

Symposium on Cystic Disease of the Breast, Rev. de chir., Paris **8**:337, 1888.

Brodie, B. C.: Lectures Illustrative of Various Subjects in Pathology and Surgery, London, Longmans & others, 1846.

Bull, W. T.: Notes on Cysts of the Breast, M. Rec. **55**:557, 1899.

Bunts, F. E.: Tumors of the Breast, Ohio State M. J. **19**:561, 1923.

Buonsanti, P.: Tumori della mammella con speciale riguardo alle lesioni precancerigne, Arch. ital. di chir. **27**:1, 1930.

Charteris, A. A.: On the Changes in the Mammary Gland Preceding Carcinoma, J. Path. & Bact. **33**:101, 1930.

Cheatle, G. L.: Cysts and Primary Cancer in Cysts of the Breast, Brit. J. Surg. **8**:149, 1920.

Cysts and Papillomata of the Breast, ibid. **9**:235, 1921.

Epithelial Hyperplasia of the Breast, Ann. Surg. **82**:673, 1925.

The Important Early Symptoms in Diseases of the Breast, Brit. M. J. **2**:47, 1927.

"Chronic Mastitis," "Cysto-Adenoma" and Adenoma of the Breast, Arch. Surg. **17**:535 (Oct.) 1928.

Clinical Signs and Indications of Changes in the Breast, Practitioner **122**:69, 1929.

A Lesion Common to Breast and Prostate Glands, Brit. J. Surg. **17**:619, 1930.

——and Cutler, M.: Tumors of the Breast, Philadelphia, J. B. Lippincott Company, 1930.

Clairmont, Paul, Denke, Wolfgang, von Haberer, Hans, and Ransi, E.: Chirurgie der Brustdrüse, Lehrbuch der Chirurgie, Berlin, Julius Springer, 1930.

Clark, A.: Swellings of the Breast, their Diagnosis and Treatment, Brit. M. J. **1**:185, 1906.

Colucci, C.: Su speciali forme di tumori cistici della mammella e sulla cura precoce del cancro mammario, Policlinico (sez chir.) **36**:285, 1929.

Cooper, A.: The Anatomy and Diseases of the Breast, Philadelphia, Lea & Blanchard, 1845.

Cori, C. F.: The Influence of Ovariectomy on the Spontaneous Occurrence of Mammary Carcinomas in Mice, J. Exper. Med. **45**:983, 1927.

Cornil, A. V.: Les tumeurs du sein, Paris, F. Alcan, 1908.

Corsy, F.: Sur l'évolution des éléments glandulaires et interstitiels dans la mamelle gravidique, et son intérêt pour l'étude des tumeurs, Bull. Assoc. franç p. l'étude du cancer **16**:383, 1927.

Creighton, C.: Cancers and Other Tumors of the Breast, Researches Showing their True Seat and Cause, London, Williams E. Norgate, 1902.

Crile, G. W.: An Analysis of 1347 Cases of Malignant Tumors of the Breast, with Special Reference to Management and End-Results, Journal-Lancet **51**:99, 1931.

Cutler, M.: Transillumination as an Aid in the Diagnosis of Breast Lesions, Surg., Gynec. & Obst. **48**:721, 1929.

The Cause of "Painful Breast," and Treatment by Means of Ovarian Residue, J. A. M. A. **96**:1201 (April 11) 1931.

The Diagnosis and Treatment of Precancerous Lesions of the Breast, Illinois M. J. **61**:313, 1932.

Davis, B. B.: Carcinoma of the Breast, with a Consideration of Pre-Cancerous Conditions, J. A. M. A. **78**:779 (March 18) 1922.

Deaver, J. B., and McFarland, J.: The Breast: Its Anomalies, Its Diseases, and their Treatment, Philadelphia, P. Blakiston's Son & Co., 1917.

Delbet, P.: Maladie kystique et mammite chronique, Bull. Soc. anat. de Paris **68**:2, 1893.

In discussion on Corsy, Bull. Assoc. franç. p. l'étude du cancer **16**:394, 1927.

Dieckmann, H.: Ueber die Histologie der Brustdrüse bei gestörtem und ungestörtem Menstruationsablauf, Virchows Arch. f. path. Anat. **256**:321 1925.

Dietrich, A.: Rückbildungsvorgänge. Fibromatose und Krebs der Brustdrüse, Deutsche Ztschr. f. Chir. **195**:145, 1926.

Drew, A. H.: Growth and Differentiation in Tissue Culture, Brit. J. Exper. Path. **4**:46, 1923.

Ellis, A. G.: Cystic Degeneration of the Mamma Showing Transformation into Scirrhous Carcinoma, Ann. Surg. **38**:336, 1903.

Erdheim, S.: Ueber die klinische Bedeutung und die pathologische Grundlage der sogenannten "blutenden Mamma," Arch. f. klin. Chir. **139**:366, 1926.

Wie sollen die mit pathologischer Sekretion aus der Mamilla einhergehenden Brustdrüsenerkrankungen operiert werden? Zentralbl. f. Chir. **54**:131, 1927.

Ernst, M.: Die physiologischen Rückbildungserscheinungen in der weiblichen Brustdrüse nach Gravidität und Menstruation, Frankfurt. Ztschr. f. Path. **31**:500, 1925.

Evans, W. A., and Leucutia, T.: Deep Roentgen-Ray Therapy of Mammary Carcinoma, Am. J. Roentgenol. **24**:673, 1930.

Ewing, J.: Neoplastic Diseases, Philadelphia, W. B. Saunders Company, 1928.

Fischer, W.: Ueber die klinische und pathologisch-anatomische Beurteilung von Geschwülsten und zystischen Veränderungen der Brustdrüse, Deutsche Ztschr. f. Chir. **192**:1, 1925.

Fitzwilliams, D. C. L.: Cancer and Cysts of the Breast, Practitioner **114**:394, 1925.

Floyd, W. O., and Haggard, W. D.: A Study of Five Hundred Breast Cases with Surgical End Results, J. Tennessee M. A. **33**:24, 1930.

Fraser, J.: A Study of the Malignant Breast by Whole Section and Key Block Section Methods, Surg., Gynec. & Obst. **45**:266, 1927.

Fray, W. W., and Warren, S. L.: Stereoscopic Roentgenography of the Breasts, an Aid in Establishing the Diagnosis of Mastitis and Carcinoma, Ann. Surg. **95**:425, 1932.

Goens-Rosales, A.: Contributions à l'étude de la glande mammaire sénile et de ses états précancéreux, Thèsie de Genève, 1919.

Goldzieher, M. A., and Kaldor, J.: Cystic Cirrhosis of the Breast, Arch. Surg. **20**:473 (March) 1930.

Greenough, R. B., and Hartwell, H. F.: Chronic Cystic Mastitis: Study of Cases, J. M. Research **9**:416, 1903.

——and Simmons, C. C.: Papillary Cystadenomata of the Breast, Ann. Surg. **45**:188, 1907.

Gross, S. W.: Tumors of the Mammary Gland, New York, D. Appleton and Company, 1880.

Hahn, E.: Die cystische Mamma und ihre Vorstufen bei jungen Frauen, Virschows Arch. f. path. Anat. **262**:531, 1926.

Harris, W. H.: Experimental Production of Carcinoma-Like Epithelial Metaplasia in Mammary Gland of Dog, Proc. Soc. Exper. Biol. & Med. **24**:522, 1927.

Hart, D.: Intracystic Papillomatous Tumors of the Breast, Benign and Malignant, Arch. Surg. **14**:793 (April) 1927.

Hellwig, C. A.: Die chirurgische Indikation bei chronischer cystischer Mastitis, Arch. f. klin. Chir. **159**:763, 1930.

Herzenberg, H.: Beiträge zur Pathogenese der Zysten Mamma, Centralbl. f. allg. Path. u. path. Anat. **39**:229, 1927.

Ingleby, H.: Relation of Fibro-Adenoma and Chronic Mastitis to Sexual Cycle Changes in the Breast, Arch. Path. **14**:21 (July) 1932.

Joel, W.: Die maladie kystique der Brustdrüse, ihre Entstehung und ihre maligne Entartung, Monatschr. f. Geburtsh. u. Gynäk. **85**:358, 1930.

Johnson, R.: Some Clinical Aspects of Carcinoma of the Breast, Brit. J. Surg. **12**:630, 1925.

Judd, E. S.: Intracanalicular Papilloma of the Breast, Journal-Lancet **37**:141, 1917.

Junge, W.: Ueber die Beziehungen zwischen der Fibrosis cystica, den gutartigen Tumoren und dem Karzinom der Brustdrüse, Beitr. z. path. Anat. u. z. allg. Path. **88**:595, 1932.

Keibel, E.: Zwei Fälle von Cystadenoma mammae, Berl. klin. Wchnschr. **41**:808, 1904.

Keynes, G.: Chronic Mastitis, Brit. J. Surg. **11**:89, 1923.

Kilgore, A. R.: Chronic Cystic Mastitis; Its Relation to Cancer of the Breast, California & West. Med. **29**:289, 1928.

Tumors and Tumor-Like Lesions of the Breast, in Association with Pregnancy and Lactation, Arch. Surg. **18**:2086 (May) 1929.

Knoflach, I. G., and Urban, K.: Zur Pathologie und Therapie der "blutenden Mamma," Arch. f. klin. Chir. **150**:355, 1928.

König: Mastitis chronica cystica, Zentralbl. f. Chir. **20**:49, 1893.

Konjetzny, G. E.: Die cystische Entartung und die Fibromatosis der Mamma und ihre Beziehung zur Krebsbildung, Med. Klin. **17**: 180, 1921.

Cystic Entartung und Fibromatose der Mamma mit Berücksichtigung ihrer Beziehung zur Krebsbildung, Zentralbl. f. Chir. **49**:1760, 1922.

Kozhevnikoff, A. I.: Morbus Reclus as a Precancerous Disease of the Mammary Glands, Mosk. med. j. (no. 3). **10**:13, 1930.

Krompecher, E.: Zur Histogenese und Morphologie der Cystenmamma, Beitr. z. path. Anat. u. z. allg. Path. **62**:403, 1916.

Landau, T.: Ueber einige Anomalieen der Brustdrüsensecretion, Deutsche med. Wchnschr. **16**:745, 1890.

Lane-Claypon, J. E.: Cancer of the Breast and Its Surgical Treatment. Report on Public Health and Medical Subjects, no. 28, London, His Majesty's Stationery Office, 1924.

Langhans, T.: Zur pathologischen Histologie der weiblichen Brustdrüse, Virchows Arch. f. path. Anat. **58**:132, 1873.

Lee, B. J.: The Therapeutic Value of Irradiation in the Treatment of Mammary Cancer, Ann. Surg. **88**:26, 1928.

Lichtenhahn, F.: Ueber Mastitis chronica cystica, Deutsche Ztschr. f. Chir. **90**:507, 1907.

Loeb, L.: Further Investigations on the Origin of Tumors in Mice, J. M. Research **40**:477, 1919.

——and Hesselberg, C.: The Cyclic Changes in the Mammary Gland under Normal and Pathological Conditions, J. Exper. Med. **25**:285, 1917.

MacCarty, W. C., and Mensing, E. H.: The Relation Between Chronic Mastitis and Carcinoma of the Breast, Collec. papers Mayo Clinic, Philadelphia, W. B. Saunders Company, 1915, vol. 7, p. 918.

McFarland, J.: Residual Lactation Acini in the Female Breast, Arch. Surg. **5**:1 (July) 1922.

McGlannan, A.: Blue-Domed Cysts and Cancer of the Breast, Arch. Surg. **21**:912, 1930.

MacNeal, W. J.: Chronic Cystic Mastitis, S. Clin. North America **12**:523, 1932.

Masson, P.: Tumeurs: Diagnostics histologiques (Séries traité de pathologie médicale et de thérapeutique appliquée, vol. 27, p. 269), Paris, A. Maloine & fils, 1923.

Miller, E. M., and Lewis, D.: Significance of a Sero-Hemorrhagic or Hemorrhagic Discharge from the Nipple, J. A. M. A. **81**:1651 (Nov. 17) 1923.

Mintz, W.: Eine histogenetisch neue Form der Mastitis chronica cystica, Berl. klin. Wchnschr. **36**:1029, 1899.

Sind wir in der Lage eine "blutende Mamma" prognostisch einzuschätzen? Med. Klin. **28**:190, 1932.

Moriconi, L. M.: Contributo allo studio della mastite cistica, Riforma med. **44**:377, 1928.

Morpurgo, B.: Beziehungen der Fibrosis cystica zu anderen Krankheiten der Brustdrüse, Verhandl. d. deutsch. path. Gesellsch. **25**:306, 1930.

Moszkowicz, L.: Ueber den monatlichen Zyklus der Brustdrüse, Arch. f. klin. Chir. **142**:374, 1926.

Oertel, H.: Involutionary Changes in Prostate and Female Breast in Relation to Cancer Development, Canad. M. A. J. **16**:237, 1926.

Orbach, E.: Beitrag zur Aetiologie der Fibroadenomatoe der Brustdrüse, Arch. f. klin. Chir. **168**:585, 1932.

Paget, J.: Lectures on Surgical Pathology, ed. 3, Philadelphia, Lindsay & Blakiston, 1865.

Peck, C. H., and White, W. C.: Tumors of the Breast, Benign and Malignant, Ann. Surg. **75**:641, 1922.

Peyron, in discussion on Corsy: Bull. Assoc. franç. p. l'étude du cancer **16**:394, 1927.

Pfahler, G. E., and Widmann, B. P.: Statistical Analysis of the Radiation Treatment of Cancer of the Breast on the Basis of the Saturation Technique, Am. J. Roentgenol. **21**:546, 1929.

Pribram, B. O.: Die pathologische Bedeutung der blutenden Mamma (reply to article by Mintz), Med. Klin. **27**:1853, 1931.

Quenu, M.: Symposium on Cystic Disease of the Breast, Rev. de chir., Paris **8**:337, 1888.

Reclus, P.: La maladie kystique des mamelles, Rev. de chir., Paris **3**:761, 1883.

La maladie kystique des mamelles, Bull. Soc. anat. de Paris **58**:428, 1883.

Symposium on Cystic Disease of the Breast, Rev. de chir., Paris **8**:341, 1888.

Robinson, H. B.: Diffuse Cystic Disease in both Breasts, Lancet **1**:622, 1896.

Rodman, J. S.: Precancerous Lesions of the Breast with Special References to Chronic Cystic Mastitis, South. M. J. **13**:348, 1920.

Chronic Cystic Mastitis; Preliminary Report on the Nature of the Process, Arch. Surg. **20**:515 (March) 1930.

Roloff: Ueber chronische Mastitis und das sogenannte Cystadenom, Deutsche Ztschr. f. Chir. **54**:106, 1899.

Rosenberg, A.: Ueber menstruelle, durch das Corpus luteum bedingte Mammaveränderungen, Frankfurt. Ztschr. f. Path. **27**: 466, 1922.

Saar, G.: Ueber Cystadenoma Mammae und Mastitis chronica cystica, Arch. f. klin. Chir. **84**:223, 1907.

Samelson, L.: Ein Beitrag zur Kenntnis der Mammacysten mit butterähnlichem Inhalt, Virchows Arch. f. path, Anat. **179**:76, 1905.

Sasse, F.: Ueber Cysten und cystische Tumoren der Mamma, Arch. f. klin. Chir. **54**:1, 1897.

Schimmelbusch, C.: Das Cystadenom der Mamma, Arch. f. klin. Chir. **44**:177, 1892.

Semb, C.: Fibro-adenomatosis cystica mammae, Acta path. et microbiol. Scandinav. **5**:62, 1928.

Sheild, A. M.: A Clinical Treatise on Diseases of the Breast, New York, The Macmillan Company, 1898.

Sicre, R.: Contribution à l'étude de la maladie kystique de la mamelle, Thèsis de Paris, no. 77, 1890.

Sistrunk, W. E.: Surgical Aspects of Benign Lesions of the Breast, New Orleans M. & S. J. **75**:47, 1922.

Stewart, J. C.: What is the Proper Surgical Treatment of Suspicious Tumors of the Involuting Breast? J. A. M. A. **43**:365 (Aug. 6) 1904.

Stiles, H. J.: Diseases of the Mammary Gland, Encyclopedia Medica, London, W. Green & Son, 1901, vol. 7, p. 277.

Syms, P.: Chronic Cystic Mastitis or Abnormal Involution of the Breast, Ann. Surg. **64**:696, 1916.

Terrier, M. F.: Symposium on Cystic Disease of the Breast, Rev. de chir., Paris **8**:341, 1888.

Terrillon, N.: Symposium on Cystic Disease of the Breast, Rev. de chir., Paris **8**:341, 1888.

Theile, P.: Zur Kenntnis der fibroepithelialen Veränderungen der Brustdrüse, Arch. f. klin. Chir. **88**:261, 1908.

Tietze, A.: Ueber das Cystadenoma mammae (Schimmelbusch) und seine Beziehungen zum Carcinom der Brustdrüse, Deutsche Ztschr. f. Chir. **56**:512, 1900.

Ueber Epithelveränderungen in der senilen weiblichen Mamma, ibid. **75**:117, 1904.

Todyo, T.: Ueber die cystische Entartung der Brustdrüse, Arch. f. klin. Chir. **104**:440, 1914.

Trelat, M.: Symposium on Cystic Disease of the Breast, Rev. de chir., Paris **8**:340, 1888.

Upcott, H.: Cystic Mammary Tumors, Practitioner **91**:14, 1913.

Velpeau, A. A. L. M.: A Treatise on the Diseases of the Breast and Mammary Region, London, Sydenham Society, 1856.

Warren, J. C.: Surgical Observations on Tumors, Boston, Crocker & Brewster, 1837.

Abnormal Involution of the Mammary Glands, Am. J. M. Sc. **133**:521, 1907.

Williams, W. R.: Monograph on Diseases of the Breast, Their Pathology and Treatment with Special Reference to Cancer, New York, William Wood & Company, 1895.

Yamagiwa, K., and Murayama, K.: Experimental Production of Mammary Carcinoma in Rabbits, J. Cancer Research **8**:119, 1924.

PEPTIC ULCERS

COMPARATIVE FREQUENCY AFTER DEPRIVATION OF BILE AND PANCREATIC JUICE

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During the past few years, in connection with other investigations, I examined a number of animals deprived of their pancreatic secretions by means of fistulas, ligation of the pancreatic ducts and pancreatectomy and was impressed by the infrequent occurrence of peptic ulcers in these animals compared with dogs in which bile was excluded. In 1926, Kapsinow [1] produced duodenal ulcers in seventeen of forty-three dogs by excluding bile from the intestine by means of cholecystonephrostomy, with ligation and division of the common duct. In 1930, Berg and Jobling [2] observed that peptic ulcers developed in ten of twenty-three dogs with biliary fistulas and biliary obstruction. Bollman and Mann [3] reported the occurrence of peptic ulcers in sixty-four of eighty-seven dogs with jaundice after ligation of the common duct. Kim and Ivy [4] found ulcers in six of ten dogs with biliary fistulas. Loewy [5a] observed duodenal ulcers in three of ten dogs deprived of bile by means of fistulas and by choledocho-ureteral anastomosis. Hosomi [6] and Ivy, Schrager and Morgan [7] found duodenal ulcers in dogs after plastic operations

From the Department of Pathology, Columbia University College of Physicians and Surgeons.

1. Kapsinow, R.: The Experimental Production of Duodenal Ulcer by Exclusion of Bile from the Intestine, Ann. Surg. **83**:614 (May) 1926.

2. Berg, B. N., and Jobling, J. W.: Biliary and Hepatic Factors in Peptic Ulcers; Experimental Study, Arch. Surg. **20**:997 (June) 1930.

3. Bollman, I. L., and Mann, F. C.: Peptic Ulcer in Experimental Obstructive Jaundice, Arch. Surg. **24**:126 (Jan.) 1932.

4. Kim, M. S., and Ivy, A. C.: Prevention of Experimental Duodenal Ulcer by Feeding Neutral Gastric Mucin, J. A. M. A. **97**:1511 (Nov. 21) 1931.

5. Loewy, G.: (*a*) Production expérimentale d'ulcères duodénaux par dérivation isolée de la bile, Bull. et mém. Soc. nat. de chir. **57**:739 (May 20) 1931; (*b*) Influence de la dérivation du suc pancréatique sur la production des ulcères duodénaux, Compt. rend. Soc. de biol. **111**:783 (Dec. 3) 1932.

6. Hosomi, K.: Ueber das sogenannte peptische Geschwür des Magens und Duodenums beim Hunde, das gelegentlich der Choledochusplastik entsteht, Virchows Arch. f. path. Anat. **267**:726 (March 21) 1928.

7. Ivy, A. C.; Schrager, V. L., and Morgan, J. E.: Spontaneous Duodenal Ulcers in Dogs with Chronic Mild Icterus and Hepatitis, Proc. Soc. Exper. Biol. & Med. **30**:698 (March) 1933.

on the common duct, which were usually accompanied by evidences of biliary obstruction.

Relatively few reports have appeared concerning the incidence of ulcers after the deprivation of pancreatic juice. Ivy and Fauley [8] found lesions in six of sixty-one animals after ligation of the pancreatic ducts. I found no changes in the stomach or duodenum in five dogs twenty-three, forty-seven, fifty-three, eighty and ninety-seven days after ligation. Dragstedt [9] observed no delay in the healing of experimental gastric ulcers or the formation of new ones in ten dogs after ligation of the minor pancreatic duct and transplantation of the major duct into the lower part of the ileum. In four dogs with pancreatico-ureteral anastomosis which had existed for sixteen, twenty-seven, thirty-four and thirty-seven days, respectively, and in one with a fistula of thirty-two days' duration Loewy [5b] found no duodenal ulceration after the prolonged loss of pancreatic juice. On the other hand, Elman and Hartmann [10] reported the occurrence of defects in the mucosa of the duodenum in all the animals of a series of six dogs with pancreatic fistulas of from thirteen to eighteen days' duration. These investigators attributed the lesions in the duodenum to the loss of the neutralizing effect of pancreatic juice on gastric acidity and minimized the importance of bile as a factor in the development of peptic ulcers in dogs.

In a series of eight depancreatized dogs which I examined sixty-one, seventy-eight, one hundred and thirty, one hundred and fifty-six, two hundred and twenty-three, two hundred and twenty-five, two hundred and fifty-eight and two hundred and seventy days after complete pancreatectomy the stomach and duodenum were normal.

The following observations were made on a series of sixteen dogs which were deprived completely of pancreatic juice by means of fistulas made according to the technic of Rous and McMaster, as adapted by Elman and McCaughan.[11] The daily ration of food, which consisted of the standard laboratory diet, was supplemented by sodium chloride administered intravenously in physiologic solution or in 5 per cent solution by stomach tube. Two dogs (36 and 58) received no additional sodium chloride, but showed a spontaneous adjustment of serum elec-

8. Ivy, A. C., and Fauley, G. B.: Factors Concerned in Determining Chronicity of Ulcers in Stomach and Upper Intestine; Susceptibility of Jejunum to Ulcer Formation; Effect of Diet on Healing of Acute Gastric Ulcer, Am. J. Surg. **11**: 531 (March) 1931.

9. Dragstedt, C. A.: Unpublished observations communicated to the author.

10. Elman, R., and Hartmann, A. F.: Spontaneous Peptic Ulcers of Duodenum After Continued Loss of Total Pancreatic Juice, Arch. Surg. **23**:1030 (Dec.) 1931.

11. Elman, R., and McCaughan, J. M.: Collection of Entire External Secretion of Pancreas Under Sterile Conditions and Fatal Effect of Total Loss of Pancreatic Juice, J. Exper. Med. **45**:561 (March) 1927.

trolytes, which will be described in detail in another paper. Although the administration of electrolytes prolonged the lives of the animals, all lost weight and after varying periods exhibited signs of profound metabolic disturbances. At postmortem examination the livers showed degenerative changes [12] consisting essentially of fatty infiltration and necrosis of the hepatic cells. The lesions varied in severity in different animals and were frequently accompanied by numerous dilated bile canaliculi. There was no obstruction of the extrahepatic bile ducts. Complete autopsies were performed on all of the animals, and histologic studies of the tissues were made. The presence of accessory pancreatic

Results of Deprivation of Pancreatic Juice in Sixteen Dogs Studied

Dog	Days of Secretion	Average 24 Hour Output of Pancreatic Juice, Cc.	Ulcers	Comment
152	12	200	0	
140	14	700	0	
153	14	300	0	
70	16	275	0	Multiple superficial mucosal erosions
89	18	200	0	
17	20	200	0	
147	20	280	0	
53	20	450	0	
49	20	300	0	Multiple superficial mucosal erosions; jaundice
156	22	225	0	
29	23	385	0	
52	25	600	+	Peritonitis due to two perforated duodenal ulcers; jaundice
36	25	300	0	
154	27	650	0	
58	31	400	0	
103	37	300	0	Jaundice

ducts and recommunication of the pancreatic duct system with the intestine were ruled out by careful dissections post mortem. The results with respect to the occurrence of ulcers and other conditions are presented in the accompanying table.

RESULTS

Analysis of the results shows that in only one instance (dog 52) were definite ulcers encountered after the loss of pancreatic juice. In this dog there were two perforated duodenal ulcers, which gave rise to diffuse peritonitis. It is interesting to note that this animal was one of three in which jaundice developed in association with marked degenerative changes in the liver.

In two animals (dogs 70 and 49) multiple small superficial erosions of the gastric and duodenal mucosa were found. I do not include such lesions within the category of ulcers, because similar changes are found in dogs under a variety of circumstances, viz., excessive vomiting, severe intoxications, infections, uremic poisoning and bilateral suprarenalectomy and as a terminal phenomenon. Until more is known concerning

12. Berg, B. N., and Zucker, T. F.: Liver Changes After Deprivation of External Pancreatic Secretion, Proc. Soc. Exper. Biol. & Med. **29**:68 (Oct.) 1931.

the etiology and development of ulcers, I believe that it is better, especially in experimental studies, to restrict the term "ulcer" to defects which involve one or more muscular layers as well as the mucosa and which correspond to the acute or chronic penetrating or perforating lesions that are encountered in man. This will diminish the confusion which exists concerning the interpretations of the results of different investigators due to the fact that no distinction is made between simple erosions and ulcers.

In some instances marked congestion of the mucosa of the duodenum and upper part of the jejunum was present.

COMMENT

My results tend to indicate that the absence of neutralization of gastric acidity by alkaline secretions, such as pancreatic juice, is not an important factor in the production of experimental peptic ulcers in dogs. This fits in with the observations of those [13] who found that gastric acidity is regulated by such factors as variations in the rate of secretion of hydrochloric acid, the amount of neutralization of the acid by bases in the mucus and food, the degree of dilution of the gastric contents, gastric motility and pyloric function, rather than by the regurgitation of alkaline duodenal fluids.[14]

Despite the fact that I employed a larger number of animals than Elman and McCaughan and that the periods of drainage were in many instances longer, the incidence of ulcers in my series of dogs was much lower than in theirs. The absence of lesions in completely depancreatized dogs which were deprived of their external pancreatic secretions for much longer periods of the time than the animals with fistulas constitutes further important evidence against the rôle of pancreatic juice in experimental ulcer formation.

In an earlier investigation [2] it was suggested that alterations in hepatic function other than the secretion of bile might be factors in the etiology of experimental peptic ulcers. Recently, Ivy, Schrager and Morgan [7] reintroduced this possibility and stressed the importance of jaundice and hepatitis in the development of ulcers in dogs with varying degrees of biliary obstruction. However, the livers of dogs deprived

13. (*a*) MacLean, H., and Griffiths, W. J.: The Automatic Regulation of Gastric Acidity, J. Physiol. **66**:356 (Dec. 20) 1928. (*b*) McCann, J. C.: Studies on the Control of the Acidity of the Gastric Juice, Am. J. Physiol. **89**:483 (Aug.) 1929. (*c*) Hollander, F., and Cowgill, G. R.: Studies in Gastric Secretion; Gastric Juice of Constant Acidity, J. Biol. Chem. **91**:151 (April) 1931. (*d*) Bolton, C., and Goodhart, G. W.: Mucus Factor in Automatic Control of Acidity of Gastric Contents, J. Physiol. **77**:287 (Feb.) 1933.

14. Boldyreff, W.: Self Regulation of Acidity of Gastric Contents and Real Acidity of the Gastric Juice, Quart. J. Exper. Physiol. **8**:1 (April 14) 1914.

of external pancreatic secretions often show marked degenerative changes,[13] although ulcers develop in only a small percentage in my experience. As present knowledge concerning the significance of pathologic changes in the liver with respect to function is limited, and as it is evident that the exclusion of bile or pancreatic juice is not a simple, isolated, experimentally induced deficiency, but involves many other complicated functional derangements, the interpretation of the mechanism underlying the tendency for peptic ulcers to develop under one set of conditions and not under others had better be deferred.

CONCLUSIONS

In a series of sixteen dogs deprived of pancreatic juice by means of fistulas for periods ranging from twelve to thirty-seven days, duodenal ulcers developed in only one animal. This animal was jaundiced and had marked degenerative changes in the liver.

In eight animals no ulcers were found in the stomach or duodenum from sixty-one to two hundred and seventy days after complete pancreatectomy.

The preponderance of evidence indicates that peptic ulcers develop more readily in dogs after the exclusion of bile than after the loss of pancreatic juice.

CHANGES IN THE BONE IN HODGKIN'S GRANULOMA

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BALTIMORE

The bone marrow is more frequently involved in Hodgkin's granuloma than is suspected, as is shown by autopsy records. Ziegler found the marrow involved in 40 per cent of the cases, while Symmers noted medullary changes in 7 of 15 cases. These authors observed a proliferation of endothelial cells, fibrosis and, in some areas, an increase in normal cell elements of the bone marrow. Other changes characteristic of Hodgkin's granuloma were present.

Actual destruction of the bone has been reported from time to time with and without roentgenographic evidence. Since the advent of the roentgen rays, groups of cases are available in which the earlier symptoms referable to the bones together with the roentgenograms can be studied, and the progress of the disease followed to its termination.

CLINICAL STUDY

Of 396 cases registered as Hodgkin's granuloma in the Memorial Hospital, the diagnosis was found to have been confirmed by biopsy or at autopsy in 172. There were demonstrable changes in the bone in 27 cases (15.7 per cent) in this group. With the exception of 1 case, the changes were demonstrated prior to the termination of the disease.

The incidence of disease of the bone in this group of cases may be compared with that reported by the authors in table 1.

Of peculiar interest is the variable duration of Hodgkin's granuloma before and after definite invasion of the bone. In 12 persons changes occurred within two years after the onset of symptoms (table 2), while in 15 the disease was evident from two to four years before the changes in the bone. At the time this report was written, 11 patients were living with changes which had existed from four months to three years. In the patients who died, skeletal changes were noted from two months to two years prior to death.

A short clinical course prior to involvement of the bone did not necessarily presage rapid termination of the disease; neither did a long clinical course preceding invasion of the bone insure the patient against rapid and fatal termination of the disease. In some persons in whom

From the Memorial Hospital for Cancer and Allied Diseases.

changes in the bones developed from one to two years after the onset of the disease the subsequent clinical course was at least equal to the interval prior to evidence of osseous changes.

The age incidence did not vary from that found in the general group of patients with Hodgkin's granuloma. The greatest age incidence was found between 17 and 40 years. The age extremes were 17 and 57 years. The ratio of males to females was about equal, and in this respect the sex incidence varied from that found in cases without involvement of the bone. In the latter group the ratio of males to females was 2.3 : 1.

Pain preceded demonstrable invasion of the bone in 17 cases. It was of a dull aching or severe and lancinating quality. It was produced either by invasion of the nerve roots, by pressure on the nerve or by the destruction of the bone. Pain was frequently referred from the lumbar region to the lower extremities, and was accentuated by changes in posture. Girdle pains were experienced with vertebral changes.

TABLE 1.—*Incidence of Osseous Changes in Hodgkin's Granuloma as Reported by Various Investigators*

	Number of Cases	Cases with Osseous Change	Per Cent
Baldridge and Awe	46	6	13.0
Uehlinger, 1933	50	17	34.0
Barron	24	5	20.8
Kimpel and Belot	33	4	12.1
Dresser	149	16	10.7

The interval between the beginning of pain and the demonstration of osseous changes extended from a few days to three years and ten months.

The record of 7 cases gave insufficient data to estimate the relationship of pain to invasion of the bone.

In many cases roentgenograms of the affected bones were made periodically, and only after a considerable time had elapsed were changes in the density of the bone noted. Frequently bones without symptoms and totally unsuspected of being diseased showed roentgenographic changes. This emphasizes the importance of complete skeletal studies in estimating the incidence of invasion of the bone by Hodgkin's granuloma.

In 1 patient (case 1) pain was present in the back for a year prior to death. Roentgenograms repeatedly gave negative results. Five months prior to death the right rectus muscle became paralyzed. At autopsy marked destruction was found in the spongy bone of the vertebrae (fig. 1). Not infrequently pain with rigidity of the spine and localized tenderness were observed, associated with vertebral changes.

Signs of compression of the cord have occurred, associated with pain. In a few instances this was noted before roentgenologic evidence pointed to vertebral change (cases 3 and 23). In 5 patients (cases 5, 6, 17 and 18) compression of the cord was observed from three weeks to two years following the appearance of changes in the bone.

The signs of compression of the cord were: weakness of the extremities below the level of compression, paraplegia, anesthesia along

Fig. 1 (case 1).—Photograph of the lumbar vertebrae removed at autopsy and bisected. It is to be noted that the intervertebral disks are intact, showing no evidence of destruction. The bodies of the vertebrae show isolated and confluent patches of Hodgkin's granuloma invading the spongiosa of the bone. There is no periosteal reaction.

the distribution of the affected nerve and hyperesthesia about the hips or shoulder girdle associated with varying degrees of numbness in the distal portions of the extremities. Occasionally atrophy of the muscles was present. Spastic paralysis was an early feature in many of the cases.

Roentgen therapy was effective in ameliorating the spinal symptoms.

In case 8 a lesion of a rib was found by routine roentgenographic examination two months before pain and swelling were observed.

Osseous changes were found by roentgenographic examination following the clinical evidence of tumor in the bones in 2 cases. In both

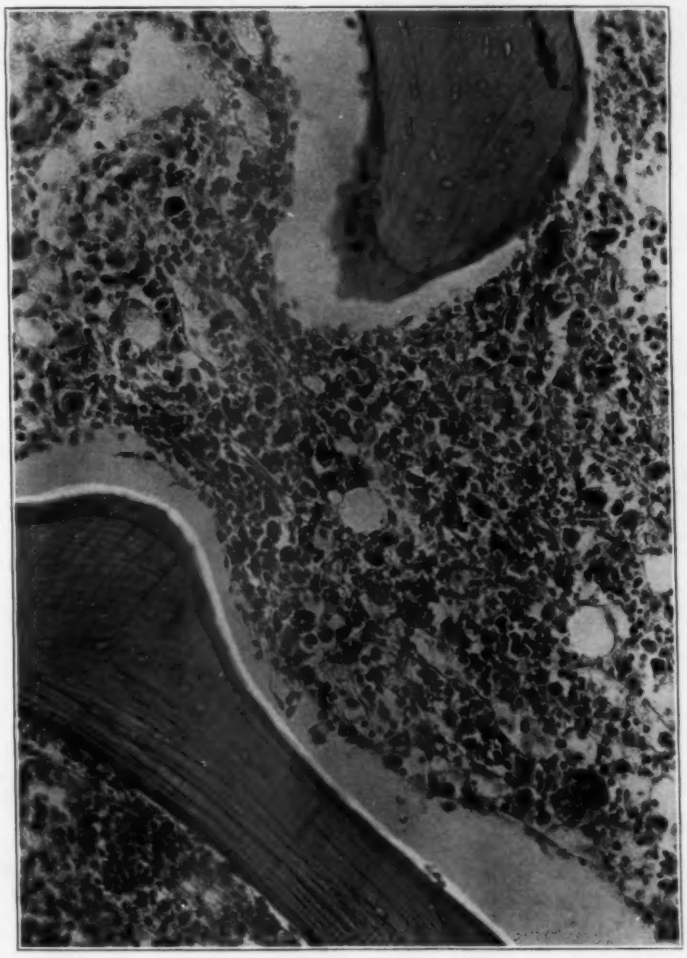

Fig. 2 (case 8).—A photomicrograph showing active Hodgkin's granuloma invading the haversian canal of a rib. Note the activity of the disease. Endothelial giant cells are present in large numbers. Many plasma cells and eosinophils are seen. There is no evidence of fibrosis. The bone shows erosion with no tendency to the formation of new bone.

instances the interval between the appearance of swelling and the making of roentgenograms was due to the tardiness of the patient in coming under observation.

In 2 patients (cases 14 and 16) herpes zoster appeared on the left side of the chest during the course of the disease. In neither patient were lesions demonstrated in the thoracic vertebrae, but both had large mediastinal masses of nodes. The cause of herpes zoster has been variously ascribed to an impingement on nerves, to infiltration of the nerves by the disease or to toxic substances reaching the nerves by circulatory paths (Voorhoeve).

Abdominal pain (cases 5, 11 and 17) led to examination of the gastro-intestinal tract. The pain proved to be referred. It arose from

Fig. 3 (case 8).—A roentgenogram depicting a cystlike area of destruction in the right sixth rib. Note the central area of destruction with trabeculations. There is some periosteal proliferation.

diseased vertebrae impinging on the nerves, or from large retroperitoneal nodes disturbing the function of the stomach.

Retroperitoneal nodes frequently cause great distortion in the viscera by displacing them, often interfering with the normal function of the gastro-intestinal tract. It must be emphasized, however, that in some cases Hodgkin's granuloma actually invades the gastro-intestinal tract, especially the stomach, ileum and cecum (Craver and Haagensen). The following case is an example of Hodgkin's granuloma invading both gastro-intestinal viscera and bone.

Case 8 (table 2).—*Autopsy.*—The body of E. N., a white youth, aged 21, was well developed but emaciated. There was no rigor mortis. The body was deeply

jaundiced. Small purpuric spots were seen over the chest and the abdomen. There was a beginning decubitus ulcer over the buttocks.

Chest: The heart, by request, was not disturbed, but the external appearance was that of acute dilatation. The pleural layers were distended with yellow, gelatinous edema. Old fibrous adhesions bound down both lungs. A moderate amount of straw-colored fluid was obtained from both pleural cavities. The lungs showed gelatinous edema throughout. No large bronchial nodes were observed. No tubercles were found in the lungs.

Abdomen: The peritoneum was edematous in its dependent portion. The mesentery of the small bowel contained three hard, yellowish calcified nodes, presumably old tubercles. The nodes along the aorta from above the celiac axis and for a short distance along the iliac vessels were all enlarged and filled with granulomatous tissue. The bulk of the disease was found in the upper part of the abdomen where there was extension into the nodes about the head of the pancreas, the bile duct and both suprarenals. The spleen weighed 480 Gm. It was of a deep purplish color and on section showed areas typical of Hodgkin's granuloma. The liver was large, bile-stained and filled with granulomatous tissue in solitary and confluent patches. The stomach showed scattered areas of Hodgkin's granuloma in the prepyloric segment. The kidneys and bladder were normal. The testicles were atrophied.

Bones: The right sixth rib appeared involved. The upper lumbar vertebrae showed hyperplastic marrow, but no positive evidence of granuloma. The marrow of the femurs was hyperplastic.

Microscopic study revealed Hodgkin's granuloma of a cellular type involving the retroperitoneal, perigastric and pancreatic nodes and the liver, spleen and stomach. Old healed calcified and fibrosed tubercles were found in the mesentery. The bone marrow of the vertebrae and femurs showed mucinous degeneration without evidence of granuloma. The rib was involved. The granulomatous process infiltrated the haversian canals and extended beneath the periosteum (figs. 2 and 3). The periosteum showed an osteoplastic reaction much like that seen in Ewing's tumor (Ewing).

CONSTITUTIONAL REACTION

The temperature varied in no particular from that found in the larger group of cases without known lesions of the bone. Fever accompanied by a slight albuminuria, was frequently associated with the disease, especially in its active phase. Though a search for Bence-Jones bodies in the urine was not a routine procedure, they were not found in the cases in which the tests were performed (cases 2, 7, 13 and 24). Several tests were made in some of the cases. Galloway reported the presence of a Bence-Jones-like protein in the urine of a patient with Hodgkin's granuloma, whose kidneys were involved. No mention was made of the condition of the bone marrow.

The blood picture ranged from a normal blood count to one showing marked secondary anemia. The white cell count varied from one showing leukopenia to a count showing marked leukocytosis. A detailed analysis of the trend in the blood picture is complicated by the effects of repeated irradiation on the blood-forming tissues. In general a moderate to severe secondary anemia was frequently found.

TABLE 2.—*Data on Twenty-Seven Cases of Hodgkin's Granuloma*

Case	Age	Sex	Duration of Disease Prior to Osseous Change	Symptoms Related to Osseous Changes (Before and After Roentgenographic Evidence)	Demonstrable Visceral and Glandular Involvement	Osseous Involvement*	Microscopic	Treatment of Bones	Laboratory Findings	Duration of Life Following Osseous Change
1	34	M	4 yrs., 4 mos.	Pain 1 yr. before; paralysis of right rectus muscle 5 mos. before	Left side of neck, left supraclavicular nodes, axillae, groins, mediastinum, retroperitoneal nodes, liver, spleen	Right femur, diffuse (C); lumbar vertebrae 1, 2, 3, 4, 5 (C)	Hodgkin's granuloma, fibrotic	Mixed low and high voltage roentgen therapy, 12/7/26 to 12/30/30	Progressive secondary anemia	Dead; changes found at autopsy
2	40	M	3 yrs., 1 mo.	Pain in bone 1 yr. before; spine rigid 1 yr. before	Right cervical node, left axilla, both groins, mediastinum	Thoracic vertebrae 11, 12 (C); lumbar vertebra 1 (C); after treatment (B)	Hodgkin's granuloma, cellular	High voltage roentgen therapy, 4/26/30 to 10/2/30	Moderate secondary anemia; Bence-Jones bodies negative	Living after 3 yrs.
3	34	M	4 yrs.	Pain 10 mos. before spinal change; flaccid paralysis 2 mos. before	General glandular enlargement; spleen palpable	Thoracic vertebrae 11, 12 (B); lumbar vertebra 1 (B)	Hodgkin's granuloma	Radium emanation pack; high voltage roentgen therapy, 8/22/28 to 10/16/28	Marked secondary anemia	Dead after 4 mos.
4	45	F	8 yrs., 10 mos.	Pain 3 yrs., 10 mos. before; rigidity of spine 6 mos. after	Bilateral cervical nodes, lateral right breast, left axilla, right groin, retroperitoneal nodes	Lumbar vertebrae 2, 3, 4 (B), with transverse processes (C); lumbar vertebra 3, partial collapse; left sacro-iliac region (B)	Hodgkin's granuloma, sarcomatous	Roentgen therapy, 6/30/28 to 12/3/30	Slight leukocytosis; normal red blood count and hemoglobin	Lost after 2 yrs., 5 mos.
5	57	M	2 yrs.	Pain 2 wks. before; abdominal pain 7 mos., 2 wks. before; intestinal symptoms 5 mos. before; signs of cord compression 4 mos. after	Right axillæ, right and left cervical nodes, inguinal regions, retroperitoneal nodes attached to vertebrae, mediastinum	Thoracic vertebra 9 (C), with collapse; sacrum (C); left 6th rib (C); pathologic fracture	Hodgkin's granuloma, cellular	Roentgen therapy	Progressive secondary anemia	Dead after 7 mos.
6	17	F	5 yrs., 4 mos.	Pain 2 mos. before; signs of cord compression 2 yrs., 1 mo. after; rigidity of spine 1 yr., 2 mos. after	Left supraclavicular nodes, suprasternal notch, mediastinum, groin	Cervical vertebra 6 (C); lumbar vertebrae 2, 3, 4 (C), with collapse; lumbar vertebra 5 (B); transverse process of lumbar vertebrae 3, 4, 5 (C); right 12th rib (C)	Hodgkin's granuloma	Radium therapy, 4/17/22 to 12/14/26; radium emanation pack, 5/15/26 to 5/28/26	Marked secondary anemia	Dead after 3 mos.
7	17	F	1 yr., 4 mos.	Pain in lumbar region 7 mos. before; signs of cord	Left and right cervical nodes, axillae	Lumbar vertebrae 1, 2, 3 (C); transverse process of lumbar	Hodgkin's granuloma	High voltage roentgen therapy, 1/8/32 to 5/12/32	Moderate secondary anemia and leukocytosis	Living after 1 yr., 8 mos.

7	17	F	1 yr., 4 mos.	Pain in lumbar region 7 mos. before; signs of cord compression 6 mos., 2 wks. after	Left and right cervical nodes, axillae	Lumbar vertebrae 1, 2, 3 (C); transverse process of lumbar vertebra 3 (C); left ilium near crest (C); right and left sacro-iliac joint regions (C;) right midischium (C)	Hodgkin's granuloma	High voltage roentgen therapy, 1/8/32 to 5/12/32	Moderate secondary anemia and leukocytosis Bence-Jones bodies negative	Living after 1 yr., 8 mos.
8	21	M	9 mos.	Pain; tumor 2 mos. after	Bilateral cervical nodes, right axilla, spleen, retroperitoneal nodes, liver, stomach, perigastric pancreatic node	Right 6th rib (C and B)	Hodgkin's granuloma, cellular	High voltage roentgen therapy, 5/13/31 to 12/3/31; Heublein unit therapy, 15% S.E.D.† 3/11/32	Progressive secondary anemia and leukopenia	Dead after 6 mos., 3 wks.
9	27	F	2 yrs., 10 mos.	Unsatisfactory data	Bilateral cervical nodes, axillae	Thoracic vertebrae 8, 9 (C), with collapse	Hodgkin's granuloma, cellular	High voltage roentgen therapy; radium emanation pack 9/29/22 to 12/5/22	Severe secondary anemia on admission with improvement after treatment	Dead after 2 yrs., 1 mo.
10	26	F	3 yrs., 7 mos.	Unsatisfactory data	Bilateral cervical nodes, axillary, inguinal and mediastinal nodes	Thoracic vertebra 12 (C); lumbar vertebrae 1, 2, 3 (C), with collapse; osteoblastic reaction about collapsed area	Hodgkin's granuloma	Radium emanation pack, 8/17/31 to to 8/22/31; injection of avian tuberculin	Severe secondary anemia with marked leukocytosis; radium treatments and blood transfusions improved blood picture	Living after 1 yr.
11	32	M	1 yr., 6 mos.	Unsatisfactory data	Left cervical nodes, mediastinum, right cervical node, axillae	Right ilium, midportion (C); left ilium near sacro-iliac margin (C); areas about acetabulae involved	Hodgkin's granuloma	High voltage roentgen therapy, 11/20/31 to 4/11/32	Moderate progressive secondary anemia; initial marked leukocytosis; transition toward normal count	Dead after 1 yr., 8 mos.
12	41	M	2 yrs.	Unsatisfactory data	Right and left supraclavicular nodes, axillae, mediastinum	Lumbar vertebra 5 (B) with transverse process (C); sacrum (B) near sacro-iliac joints; right ilium central (C); left ilium central (C)	Hodgkin's granuloma, cellular	High voltage roentgen therapy, 3/21/30 to 3/30/32	Initial leukocytosis reverting to normal	Living after 11 mos.
13	20	M	1 yr., 2 mos.	Pain 1 yr., 3 wks. before	Left cervical nodes, axillae, over left clavicle and right scapula	Frontal bone (C); lumbar vertebrae 1, 2, 3, 4, 5 (B)	Hodgkin's granuloma	High voltage roentgen therapy, 1/31/31 to 8/28/31; Heublein unit therapy, 30% S.E.D., 2/27/32	Moderate secondary anemia following Heublein therapy; transfusion followed by leukocytosis and increase in red count; Bence-Jones bodies negative	Living after 7 mos., 2 wks.

* Osteoclastic involvement is indicated by (C); osteoplastic, by (B).
† S.E.D. indicates skin erythema dose.

TABLE 2.—*Data on Twenty-Seven Cases of Hodgkin's Granuloma—Continued*

Case	Age	Sex	Duration of Disease Prior to Osseous Change	Symptoms Related to Osseous Changes (Before and After Roentgenographic Evidence)	Demonstrable Visceral and Glandular Involvement	Osseous Involvement*	Microscopic	Treatment of Bones	Laboratory Findings	Duration of Life Following Osseous Change
14	17	M	1 yr., 6 mos.	Pain in pelvis 20 days before; pain in upper tibia 4 mos., 2 wks. before; tumor in region of left buttock 8 mos. after	Mediastinum, left and right cervical nodes, inguinal nodes, spleen	Right ilium near sacro-iliac joints and wings (B); ischia (B); pubes (B;) tibia (C)	Hodgkin's granuloma; some fibrosis	High voltage roentgen therapy, 7/18/30 to 3/16/32	Admitted with moderate secondary anemia and normal white blood count; anemia improved and leukocytosis developed	2 yrs., 5 mos. dead
15	40	F	3 yrs., 6 mos.	Pain 8 mos. before in left ilium, femur; pain a few weeks before in right ilium	Right cervical nodes right supraclavicular nodes, axillae, inguinal nodes	Left ilium (C); right ilium (C); left femur (C); thoracic vertebrae 4, 5 (C)	Hodgkin's granuloma, cellular	High voltage roentgen therapy, 3/1/30 to 11/9/31	Unsatisfactory data	Dead after 2 yrs., 2 wks.
16	19	M	1 yr., 4 mos.	Tumor 13 mos., 2 wks. before roentgenogram was made	Left upper lung, mediastinum, left and right cervical nodes, axillae, spleen	Left 2d rib (C)	Hodgkin's granuloma, fibrotic	Radium emanation pack, 4/17/28 to 5/15/28; high voltage roentgen therapy, 6/14/28 to 8/29/29	Normal red blood count and hemoglobin; moderate leukocytosis; normal toward end of life	Dead after 1 yr., 9 mos.
17	33	M	1 yr., 6 mos.	Abdominal pain 8 mos., 21 days before; pain in spine 9 mos., 2 wks. before; pain in left humerus 4 mos., 2 wks. before; signs of cord compression 3 mos. after	Left cervical nodes, spleen	Thoracic vertebrae 11, 12 (B); lumbar vertebrae 1, 2 (B); left humerus (C)	Hodgkin's granuloma, cellular	High voltage roentgen therapy, 9/10/28 to 5/14/29	Moderate secondary anemia	Dead after 1 yr., 2 wks.
18	24	M	8 mos.	Pain 7 mos. before; symptoms of cord compression 3 wks. after	Mediastinum, right and left supraclavicular nodes, axillae, groins, spleen, liver	Left humerus (C); lumbar vertebra 2 with transverse process (C); lumbar vertebrae 4,5 (B)	Hodgkin's granuloma	High voltage roentgen therapy, 4/10/28 to 12/26/28; 3 transfusions	Marked secondary anemia with some improvement; normal white blood count, on one occasion low; reason, treatment	Dead after 9 mos., 2 wks.
19	28	F	5 yrs., 3 mos.	Pain 10 mos. before in right femur; pain 1 mo. before in left femur; pain 1 yr., 6 mos. before in pelvis	Mediastinum, left and right cervical nodes, right supraclavicular nodes, spleen	Left femur, upper third (C); left femur, midshaft (B); ilia about sacro-iliac joints (C); right femur, upper third (C)	Hodgkin's granuloma; some fibrosis	High voltage roentgen therapy, 10/22/28 to 4/29/31; 1 transfusion	Progressive secondary anemia; intermittent leukocytosis; anemia improved after treatment and transfusion	Dead after 1 yr., 7 mos.

20	21	F	1 yr., 3 wks.	Pain in femurs 5 mos. before; pain in upper left tibia 2 mos., 2 wks. before; pain in left side of abdomen 3 mos. before changes in left ischium	Mediastinum, left and right cervical nodes, right axilla, spleen	Left and right femur C); left tibia (C)	Hodgkin's granuloma	High voltage roentgen therapy, 4/3/29 to 10/2/29	Progressive secondary anemia	Dead after 2 mos., 3 wks.
21	40	F	3 yrs., 1 mo.	Unsatisfactory data	Mediastinum, right and left cervical nodes, right and left supraclavicular nodes, axillae, spleen	Lumbar vertebrae 1, 2, 3, 4, 5 (B); pelvic bones (B); right and left femur (C)	Hodgkin's granuloma, cellular	High voltage roentgen therapy, 5/18/32 to 5/25/32; tuberculin injections	Slight leukocytosis; urine and Bence-Jones bodies negative	Living after 1 yr.
22	16	F	5 mos.	Pain in left humerus 5 mos. before; pain in right upper humerus 9 mos. after; pain in upper tibia 1 yr. before	Mediastinum, left supraclavicular nodes, left axilla	Left humerus (C); right humerus (C); left 6th rib (C); pathologic fracture 6th rib	Hodgkin's granuloma; some fibrosis	High voltage roentgen therapy, 10/22/31 to 3/11/32; Hueblein unit therapy, 25% S.E.D., 4/6/32	Moderate secondary anemia; terminal leukocytosis; Bence-Jones bodies negative	Failing after 7 mo., 2 wks.
23	27	M	3 yrs., 7 mos.	Signs of cord compression 7 mos., 1 wk. before; pain 6 mos., 1 wk. before in vertebrae	Mediastinum, right and left cervical nodes, right axilla, spleen, groins, mesenteric glands	Thoracic vertebrae 10, 11 (B); right ischium, right pubis (C)	Hodgkin's granuloma, cellular	High voltage roentgen therapy to general regions not specifically directed to bones	Moderate leukocytosis	Living after 1 yr., 1 mo.
24	61	F	4 yrs., 6 mos.	Pain immediately before	Mediastinum, right supraclavicular nodes, axillae, groins	Frontal bone (C)	Hodgkin's granuloma	Low voltage roentgen therapy, 9/26/30 to 10/3/30; Heublein unit, 6/9/32	Blood, no abnormal change; Bence-Jones bodies negative	Living 9 mos., 2 wks.
25	57	F	2 yrs., 8 mos.	Tumor 4 mos. before	Mediastinum, left and right cervical nodes, right axilla, right inguinal nodes	Sternum, lower third (C and B)	Hodgkin's granuloma, cellular	Hueblein unit therapy, 15% S.E.D.; 1 high voltage roentgen treatment	Moderate progressive secondary anemia; intermittent leukopenia	Living after 4 mos., poor condition
26	48	F	4 yrs., 2 mos.	Unsatisfactory data	Mediastinum, right and left cervical nodes	Parietal bone (C)	Hodgkin's granuloma	Erysipelas and prodigiosus toxins (Coley's)	Moderate leukocytosis	Dead after 1 yr., 6 mos.
27	30	M	10 yrs.	Unsatisfactory data	Right and left cervical nodes, tonsils	Right ribs 1, 2, 3, 4 near sternum (C)	Hodgkin's granuloma	Radium emanation pack, 9/17/23 to 9/22/23; low voltage therapy, 11/9/23 to 3/18/24 and 11/13/24 to 1/19/26	Unsatisfactory data	Living after 5 mos., 1 wk.

Improvement in the anemia followed irradiation of the diseased bones or lymph nodes, unless the marrow received a dose of roentgen therapy which temporarily inhibited the formation of blood. Osseous involvement did not materially alter the blood picture from that generally seen in the disease.

Leukocytosis was often observed during the course of the disease. The differential count of the white blood cells showed polymorphonuclear neutrophils ranging from 38 to 90 per cent. In 20 cases, from 1 to 6 eosinophils were observed in individual blood counts. Leukopenia, when present, usually followed substantial irradiation. A leukocytosis was often reduced to a relatively normal level by irradiation. The treatment causing a reduction in the white blood cells was not always directed toward the osseous system. The terminal phases of the disease revealed a progressive emaciation and anemia.

OSSEOUS INVOLVEMENT

A review of the literature[1] indicates that vertebral changes are most frequent. The bones involved in the order of their frequency were: vertebrae, sternum, pelvis, femur, ribs, skull, humerus, scapula and clavicle. Few reports dealt with lesions of other bones.

Among our own patients the bones most constantly affected were those of the spine and pelvis (table 3 and fig. 4). Pathologic fracture was rare. In cases 5 and 22 a rib was fractured. In case 22 partial collapse existed in the head of the left humerus together with fracture.

Collapse of the diseased vertebrae was commonly observed (table 2).

Roentgen Studies.—The osseous lesions as depicted by roentgenograms were either predominantly osteoplastic (fig. 5) or osteoclastic (fig. 6). In the long pipe bones the involved portion was usually situated near the proximal end. As the disease progressed, the entire bone was frequently involved. When one considers that Hodgkin's granuloma appears early in the hematopoietic tissues, the reason for this distribution of osseous invasion becomes apparent. Piney, in 1922, made an anatomic and histologic analysis of the bone marrow. He found that at birth all of the skeleton except the cranium contained red marrow. As the person's age increased, fatty deposits replaced the marrow gradually. In the adult, the vertebrae, sternum and pelvis and most of each rib contained red marrow. The only red marrow in the long bones was found at the upper ends of the diaphyses.

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1. The review of the literature includes all the biliography with the exception of the references to: Copeland and Geschickter, Ewing, Craver and Haagensen, Galloway, Piney and Voorhoeve.

Fig. 4.—Diagram showing the distribution of Hodgkin's granuloma in the skeleton. The black areas represent the most frequent sites of invasion; the checkered areas, the common sites of involvement; the diagonal lines, the occasional areas invaded, and the white areas, the rarely invaded portions of the bones.

TABLE 3.—*Involvement of Bone in Twenty-Seven Cases of Hodgkin's Granuloma*

	Number of Cases	Number of Times	Right	Left
Vertebrae				
Cervical 6	1	1	..	..
Thoracic 8	1	1	..	..
Thoracic 9	2	2	..	..
Thoracic 10	1	1	..	..
Thoracic 11	4	4	..	..
Thoracic 12	4	4	..	..
Lumbar 1	8	8	..	..
Lumbar 2	9	9	..	..
Lumbar 3	7	7	..	..
Lumbar 4	7	7	..	..
Lumbar 5	7	7	..	..
Pelvis				
Ilium	7	12	6	6
Ischium	3	4	3	1
Pubis	2	3	2	1
Sacro-iliac joint	2	3	1	2
Sacrum	2	2	..	..
Femur				
Upper third	2	3	2	1
Mid third	3	3	1	2
Lower third	1	2	1	1
Humerus				
Upper third	2	3	1	2
Mid third	1	1	..	1
Tibia (upper third)	2	3	1	2
Ribs 1	2	1	1	..
2	2	2	1	1
3	1	1	1	..
4	1	1	1	..
6	3	3	1	2
12	1	1	1	..
Skull				
Frontal bone	2	2	..	..
Parietal bone	1	1	..	..
Sternum (lower third)	1	1	..	..

A progression of the disease was found to accentuate further the two varieties of osseous change already mentioned. In many cases destruction of bone and the production of new bone accompanied each other.

Fig. 5 (case 19).—A roentgenogram showing Hodgkin's granuloma invading both the left and the right femurs. The lesions of the left femur simulated Garré's osteomyelitis with thickening of the cortex, a proliferation of the periosteum and a tendency to obliterate the marrow cavity. The right femur in its upper portion shows a small area of central destruction with some thickening of the medial cortex and a slight periosteal reaction about the area of involvement.

Roentgenograms of the skull in this series presented a predominant osteoclastic reaction. The areas of destruction were surrounded by varying degrees of increased density, representing new bone.

Involvement of the larynx with extension to the cartilage has been reported (Askanazy, 1931). We have not seen such an invasion by Hodgkin's granuloma.

In case 25, the sternum, a bone in close approximation to involved mediastinal nodes, showed a marked periosteal reaction (fig. 7) with cortical destruction of the bone and with little tendency to the formation of new bone.

Fig. 6 (case 12).—Roentgenogram of the left ilium showing a central area of destruction. In the distal portion of the ilium small areas of destruction are seen with areas of increased density about them. These areas suggest an overlying lymph node affected by Hodgkin's granuloma infiltrating directly into the bone. The areas of increased density represent an attempt on the part of the bone to wall off the disease process.

The lesions in the rib in all instances appeared much like metastatic processes with marked destruction. In case 8 (fig. 3), when first observed in the roentgenograms the lesion appeared much like a cyst of the bone.

There was marked central destruction with a periosteal reaction and the formation of new bone which appeared like a shell about the diseased bone.

The vertebrae either showed complete destruction with partial collapse or appeared sclerosed, with or without collapse. Sclerosis of the

Fig. 7 (case 25).—Roentgenogram showing invasion of the lower portion of the sternum by Hodgkin's granuloma. There are periosteal proliferation and cortical destruction with practically no formation of new bone. Many of these cases represent direct infiltration from mediastinal nodes involved by the disease.

vertebral bodies and osteolytic changes in the transverse processes were often depicted in the same roentgenogram. As many as three or four vertebrae were found partially collapsed, one on the other, giving the

appearance of one or two diseased vertebrae rather than four (fig. 8). Dresser, who has made a study of this feature, found that the intervertebral disks were intact despite the fact that the bone was destroyed about them. Uehlinger found that the intervertebral disks were sometimes crushed and broken. In some instances the disks showed step formation due to peculiarities of osseous destruction.

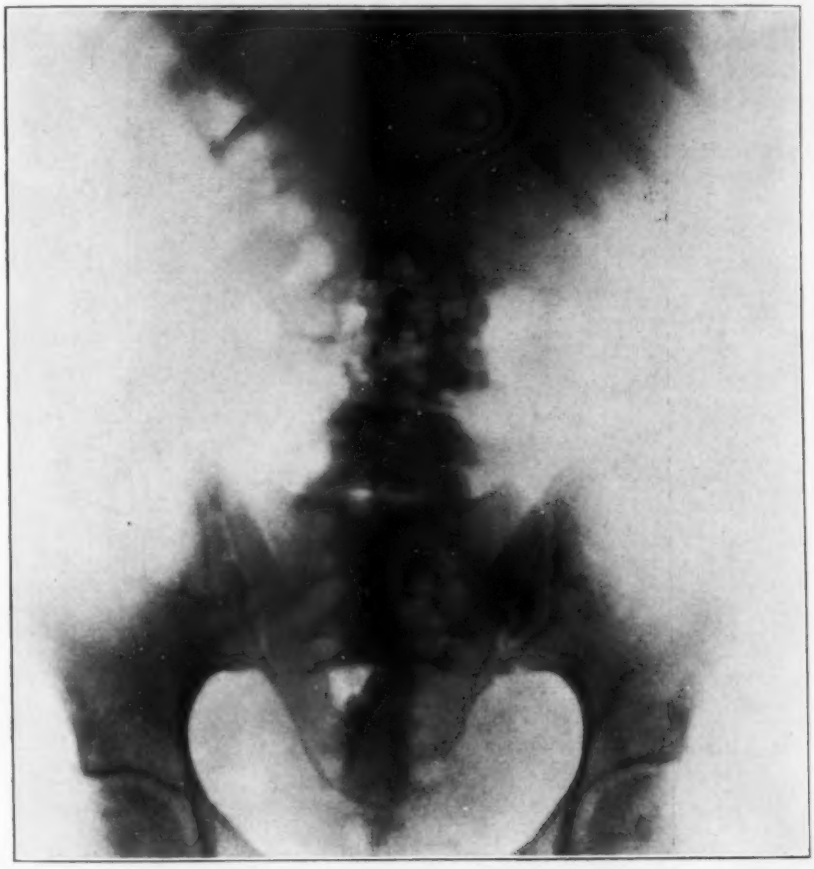

Fig. 8 (case 7).—Roentgenogram showing marked destruction of the third and fourth lumbar vertebrae. Partial collapse of the vertebrae is noted. Periosteal proliferation together with some formation of new bone is seen. There is increased density of the fifth lumbar vertebra. The transverse processes of the fifth lumbar vertebra show osteolytic involvement.

The periosteum of the vertebrae was frequently raised. The subperiosteal proliferation varied in amount and was often associated with collapse of the vertebrae.

Evidences of spinal osteo-arthritis were occasionally observed, and while not a specific expression of the disease process, the osteophytes formed were involved occasionally by Hodgkin's granuloma (fig. 9). In case 4 the first roentgenograms revealed only the features of an osteo-arthritis with marked lipping of the vertebrae. Later roentgeno-

Fig. 9 (case 18).—Roentgenogram of the lumbar spine showing evidences of osteo-arthritis about the second, third and fourth lumbar vertebrae. The second and fourth lumbar vertebrae show increased density with some areas of rarefaction. The bridging process between the vertebrae may become involved by the disease.

grams demonstrated a bridging process between the third and fourth transverse processes of the lumbar vertebrae. In the center of this bony bridge an area of destruction was seen. Still later films revealed marked destruction of the third and fourth lumbar vertebrae.

The pelvis, lying in close proximity to lymph nodes, frequently showed combined sclerotic and osteolytic features. The majority of lesions appeared in the wings of the ilia or about the sacro-iliac joints. Osteolytic areas were surrounded by areas of increased density (fig. 6). The acetabula were less frequently involved than was expected.

In the long bones, such as the humerus, a destructive area appearing in the upper end of the bone just beneath the periosteum was common.

Fig. 10 (case 22).—Roentgenogram showing marked destruction of the head of the humerus. Note the pathologic fracture and partial collapse. Below the area of destruction small areas of rarefaction may be seen in the shaft. The periosteum is lifted by the disease process and gives an appearance somewhat similar to the onion-peel formation frequently seen in Ewing's tumor.

Infiltration was the rule, causing partial collapse of the diseased bone with fracture (fig. 10). The disease infiltrated beneath the periosteum, lifting it from the cortex. A central destructive process involving the cortex was often seen (fig. 11). Some lesions simulated Garré's non-

suppurative osteomyelitis (fig. 5). The cortex was thickened with or without small foci of rarefaction. A definite periosteal proliferation was present and blended with the cortical thickening. The earliest osseous change found was either a slight increase in the density or a porosity of the entire bone. The earlier changes were difficult to establish as definite involvement of the bone.

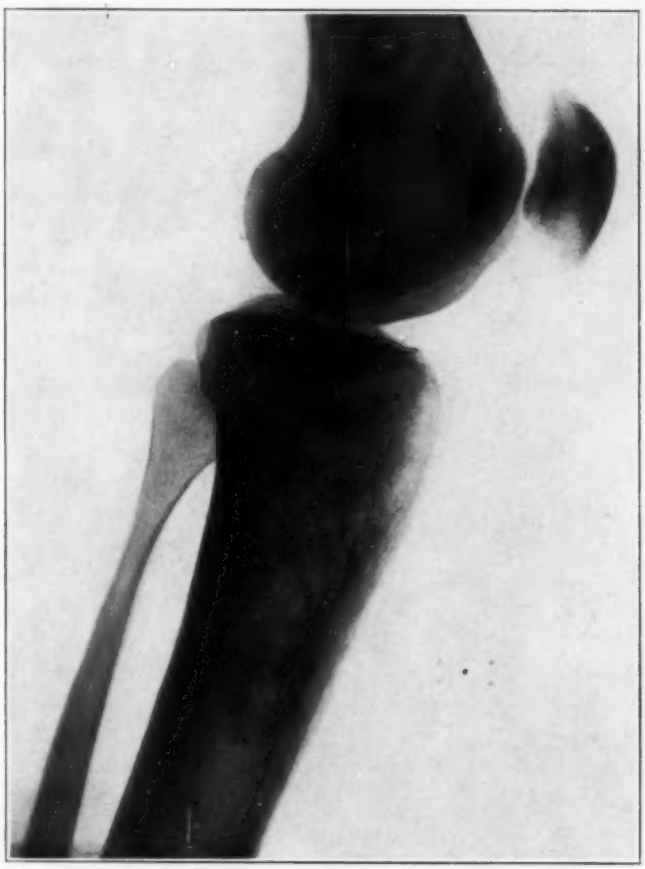

Fig. 11 (case 14).—Roentgenogram showing the upper end of the tibia involved by a central destructive process. Areas of increased density may be seen around the areas of destruction. The entire upper end of the tibia shows rarefaction.

GROSS MATERIAL AND MICROSCOPIC EXAMINATION

In all cases under observation biopsies of the cervical, axillary or inguinal nodes were done. Complete autopsy was performed in 2 cases. In case 1 (fig. 1) the diseased lumbar vertebrae were obtained, and on cross-section showed discrete and confluent patches of Hodgkin's granuloma, the process infiltrating the spongy bone of the vertebrae.

No periosteal reaction was seen. The intervertebral disks were not involved. In case 8 (figs. 2 and 3) one rib showed a lifting of the periosteum with proliferation of granulomatous tissue beneath it. On bisection, the rib showed a central destructive area with some reactive bone about it. Granulomatous tissue beneath the periosteum coalesced with the reactive bone. The marrow from the vertebrae and femur of the same case showed mucinous degeneration but no evidence of Hodgkin's granuloma. The marrow in the rib near the lesion was in large part replaced by the granulomatous process. In the more remote portions of the rib the marrow was hyperplastic.

A histopathologic study of the lymph nodes showed changes varying from those of Hodgkin's granuloma with marked fibrosis (case 1) to those of Hodgkin's granuloma with sarcomatous features (case 5). The greater number of the cases showed a cellular granuloma with a moderate number of endothelial giant cells, proliferation of endothelium infiltration by eosinophils and some plasma cells. Varying degrees of fibrosis were noted. Unfortunately, the biopsy specimens usually were not taken at the time the lesions of the bone were first observed. It is therefore impossible to estimate the activity of the disease at the time the bone was involved. In case 1 invasion of the bone was noted at autopsy and yet could not be demonstrated in the roentgenograms. In this case the Hodgkin granuloma was of the fibrotic type. In case 16, in which histopathologic changes were of a similar type, osseous changes in the rib were easily demonstrated roentgenographically and proved to be osteolytic.

It is evident from the duration of the disease before and after the changes in the bone that its activity varied in different patients. It is noteworthy that histopathologic studies may show varying degrees of activity in different tissues of the same patient.

Of importance is the fact that where diseased lymph nodes lie in close approximation to the bones there is often found a direct extension from the nodes to the bone. This is seen especially about the sternum, vertebrae and pelvis. The changes in the bone, however, do not seem to be altered because of a different mode of involvement.

DIFFERENTIAL DIAGNOSIS

Hodgkin's granuloma affecting bone may be confused with metastatic deposits in the bone from carcinoma, neoplastic processes such as lymphosarcoma and the leukemias. Ewing's tumor may be simulated during certain phases of the osseous invasion. Less frequently the condition has been confused with various forms of osteomyelitis, including Garré's osteomyelitis. In one case a lesion of the rib had many of the characteristics of a cyst of the bone.

A careful physical examination of the patient will do much to obviate mistaken diagnosis.

Varying degrees of involvement of the lymph nodes, with enlargement of the spleen, itching and secondary anemia, are characteristic of Hodgkin's granuloma. A biopsy is made with little difficulty in the majority of cases.

Metastatic carcinoma as a rule shows central destruction of bone without the production of new bone. A periosteal reaction is usually lacking. In two types of metastases to the bone, however, an osteoplastic reaction may predominate, i. e., in metastases from the prostate and the breast. Such reactions are more apt to be confused with Hodgkin's granuloma.

Lymphosarcoma may cause similar changes in the bones. A biopsy is of great importance in distinguishing between the two diseases. The spleen is less likely to be involved in lymphosarcoma, and many of the constitutional symptoms of lymphogranuloma are absent.

The leukemias are discovered by studies of the blood. A routine examination of the blood should be made in cases in which there are osseous lesions. The bones may show only osteoporosis in the roentgenogram, or osteoplastic features may predominate, with or without periosteal reaction. These features of osseous invasion are often seen in Hodgkin's disease.

In osteomyelitis, adenopathy and enlargement of the spleen are lacking. The leukocyte count may be of value if it is high. It is to be remembered, however, that in Hodgkin's granuloma a moderate leukocytosis is frequently present and rarely there may be a marked leukocytosis. A sequestrum with a shaggy periosteal reaction characterizes the usual case of osteomyelitis. In atypical osteomyelitis a biopsy may be necessary to establish its identity. Garré's nonsuppurative osteomyelitis has been simulated by Hodgkin's disease (fig. 5). The other features of the disease should serve to distinguish it from nonsuppurative osteomyelitis.

TREATMENT

Despite valuable adjuncts, such as heliotherapy, a regimen such as is given in tuberculosis, large doses of arsenic, transfusions and the experimental use of various serums, filtrates or avian tuberculin, the main reliance in the treatment of Hodgkin's disease continues to be on irradiation, with either gamma or roentgen rays, preferably the latter in most cases.

Various methods of irradiation have been suggested and tried by different workers. Some irradiate with single heavy doses; others prefer protracted fractional irradiation. Some follow a routine of irradiation of nearly all the lymph node-bearing areas, regardless of demonstrable implication in the disease process; others have contented themselves with treating on a purely symptomatic basis.

In general, it appears that patients do not tolerate well a routine heavy irradiation of all the lymph node areas, and, on the other hand, failure to secure satisfactory palliation in the past has often been due to neglect of treatment of certain areas such as those containing the deeper nodes. In recent years at the Memorial Hospital we have employed almost exclusively high voltage roentgen rays, either in suberythema or in fractional doses, depending on the local and general condition of the patient, and have paid much more attention than formerly to the treatment of the mediastinal and retroperitoneal regions, when there was demonstrable or presumable involvement of those areas. No routine dosage is applied. Each case is individualized. The treatment regarded as best is that which will secure the best palliation for the longest time. The treatment should never be so severe as to make it seem harder to bear than the disease. The skin should be spared severe reaction. In the last two years we have found Heublein's method of prolonged continuous low intensity irradiation of the entire body to be a valuable part of the treatment in a number of cases.

The gross lesions of the bones may be treated to good advantage either by single large suberythema doses or by fractional doses of high voltage roentgen rays. Relief from pain is often prompt, and reparative processes may be demonstrated in some cases. In the terminal stages, however, we do not attempt routine irradiation of all the bones, although it is well known that the marrow is usually diffusely involved, as in such cases a severe degree of anemia and sometimes leukopenia already exists and would only be aggravated by irradiation.

SUMMARY

1. One hundred seventy-two patients with Hodgkin's granuloma, proved histologically, have been studied.

2. Twenty-seven patients (15.7 per cent) were found to have involvement of the bone.

3. The bones most frequently involved were found to be those of the spine and pelvis.

4. Pathologic fracture was found to be rare, but collapse of the vertebrae was frequent.

5. Two types of osseous changes were noted: osteoplastic and osteolytic. A combination of both was seen in many cases.

6. Two routes of osseous involvement may be assumed: (1) from the marrow foci of Hodgkin's granuloma; (2) from the contiguous diseased lymph nodes from which direct infiltration into bone occurred.

7. The intervertebral disks were rarely involved.

8. No relationship between the structure of the lymph nodes and the type of osseous change could be demonstrated.

BIBLIOGRAPHY

Achard, C.: Malignant Granuloma with Pleural Onset, Rev. gén. de clin. et de thérap. **45**:177, 1931.

Arnell, S.: Two Cases of Hodgkin's Disease with Bone Destruction, Acta radiol. **8**:259, 1927.

Askanazy, M.: Verhandl. d. deutsch. path. Gesellsch. **15**:86, 1912.

Lymphogranuloma of the Bone Marrow, Centralbl. f. allg. Path. u. path. Anat. **31**:557, 1920-1921.

Lymphogranulomatosis, J. de méd. de Paris **51**:170, 1931.

Baldridge, C. W., and Awe, C. D.: Lymphosarcoma: A Study of 150 Cases, Arch. Int. Med. **45**:161 (Feb.) 1930.

Barron, M.: Unique Features of Hodgkin's Disease (Lymphogranulomatosis), Arch. Path. **2**:659 (Nov.) 1926.

Béclère, A.: Bone Lesions in Malignant Granuloma or Hodgkin's Disease, Bull. et mém. Soc. de radiol. méd. de France **12**:140, 1924.

Note on the Participation of the Skeleton in the Localizations of Malignant Granuloma, Bull. et mém. Soc. méd. d. hôp. de Paris **48**:961, 1924.

Beitzke: Demonstration of Preparations of a Multiple Megakarocytic Granuloma, Verhandl. d. deutsch. path. Gesellsch. **13**:224, 1909.

Belot, J.; Nahan, L., and Kimpel, J.: Involvement of Bones in the Course of Malignant Granulomatosis, J. de radiol. et d'électrol. **12**:257 (June) 1928.

Burnham, C. F.: Hodgkin's Disease: With Especial Reference to Its Treatment by Irradiation, J. A. M. A. **87**:1445 (Oct. 30) 1926.

Cone, S. M.: Bone in Hodgkin's Disease, J. Bone & Joint Surg. **25**:458, 1927.

Copeland, M. M., and Geschickter, C. F.: Ewing's Sarcoma, Arch. Surg. **20**:246 (March) 1930.

Craver, L. F., and Haagensen, C. D.: A Note on the Occurrence of Herpes Zoster in Hodgkin's Disease, Lymphosarcoma and the Leukemias, Am. J. Cancer **16**:502, 1932.

Delius, L.: Compression of Spinal Cord by Lymphogranuloma, Deutsche Ztschr. f. Nervenh. **125**:142, 1932.

Dresser, R.: Lymphogranuloma of Bones, Strahlentherapie **41**:401, 1931.

Düring, M.: On the Pathology and Clinical Features of Lymphogranuloma, Deutsches Arch. f. klin. Med. **127**:76, 1918.

Ewing, J.: Neoplastic Disease, ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 40.

Fränkel, E.: Lymphomatosis Granulomatosa, in Henke, F., and Lubarsch, O.: Handbuch der speciellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 1, p. 349.

——and Much, H.: Further Researches in Lymphogranulomatosis, Ztschr. f. Hyg. u. Infektionskr. **99**:391, 1923.

Friedrich, H.: Lymphogranulomatosis (Hodgkin's Disease) of the Bones, Fortschr. a. d. Geb. d. Röntgenstrahlen **41**:206 (Feb.) 1930.

Galloway, J.: Remarks on Hodgkin's Disease, Brit. M. J. **2**:201, 1922.

Gilbert, R.: On the Subject of Bone Alteration in Malignant Granuloma, Bull. et mém. Soc. de radiol. méd. de France **13**:93, 1925.

——and Sluys, F.: The Radiotherapy of Malignant Granuloma, J. de radiol. et d'électrol. **17**:129, 1933.

Goormaghtigh, N.: Spinal Cord Complications in Lymphogranuloma and Lymphosarcoma, Bull. Acad. roy. de méd. de Belgique **12**:116 (Feb. 27) 1932.

Grudzinsky, Z.: Vertebral Lymphogranulomatosis, Virchows Arch. f. path. Anat. **288**:36, 1933.

Hare, D. C.; Lepper, E. H., and Weber, F. P.: Two Cases of Lymphogranulomatosis Maligna, Lancet **1**:334 (Feb. 13) 1932.

Hauck, G.: A Contribution to the Knowledge of Hodgkin's Disease, Centralbl. f. allg. Path. u. path. Anat. **29**:225, 1918.

Hollborn, R.: Statistical Review of Cases of Lymphogranulomatosis Observed at the Medical Clinic in Leipzig, Years 1910-1927, Inaug. Dissert., Leipzig, 1928.

Hulten, O.: A Case of Ivory Bone in Lymphogranulomatosis, Acta radiol. **8**:245, 1927.

Jenkinson, E. L.: Hodgkin's Disease, Radiology **19**:41, 1932.

Johnston, J. M.: Hodgkin's Disease with Invasion of Spinal Column: Pressure of Cauda Equina; Degeneration of Posterior Columns of Cord, Pennsylvania M. J. **34**:877, 1930-1931.

Joly, M.: Bone Lesions in Lymphogranulomatosis, Bull. et mém. Soc. de radiol. méd. de France **19**:45, 1931.

Kimpel, J.: Localisations osseuses au cours de la granulomatose maligne, Paris, Amédée Legrand, 1927.

——and Belot, J.: Bone Involvement in the Course of Malignant Granuloma, Transactions International Congress of Radiology, Paris, Masson & Cie, 1931, p. 81.

Kremser, K.: On Bone Changes in Hodgkin's Disease, Röntgenpraxis **2**:998, 1930.

Lemierre, A., and Angier, P.: Vertebral Localization in Course of Malignant Lymphogranulomatosis: Dislocation of Cervical Spine with Compression of Cord; Case, Ann. d'anat. path. **8**:916, 1931.

Levin, I.: Lymphoma Malignum (Hodgkin's Disease) and Lymphosarcoma; Pathogenesis, Radiotherapy and Prognosis, J. A. M. A. **96**:421 (Feb. 7) 1931.

Lockwood, I. H.; Johnson, E. T., and Narr, F. C.: Hodgkin's Disease with Bone and Skeletal Muscle Involvement, Radiology **14**:445, 1930.

Louste, Thibaut and Valière-Vialeix: On a Case of Hodgkin's Disease Which Presented Bone Lesions During the Course of the Disease, Difficult of Interpretation: Improvement of the Lesions Under the Influence of Radiotherapy, Bull. et mém. Soc. méd. d. hôp. de Paris **48**:761 (May 23) 1924.

Lyon, M. W., Jr.: Case of Mediastinal Hodgkin's Granuloma, with Perforation of the Chest Wall, Am. J. M. Sc. **158**:557, 1919.

Montgomery, A. H.: Hodgkin's Disease of Bones, Ann. Surg. **87**:755, 1928.

Naegeli, O.: Blutkrankheiten und Blutdiagnostik, Lehrbuch der klinischen Hämatologie, ed. 3, Berlin, Walter de Gruyter & Co., 1919, p. 518.

Pfahler, G. E., and O'Boyle, C. P.: A Case of Hodgkin's Disease with Late Development of Sacro-Iliac Disease, Cured by Roentgen Treatment, Am. J. Roentgenol. **11**:406, 1924.

Piney, A.: Carcinoma of the Bone Marrow, Brit. J. Surg. **10**:235, 1922-1923.

Robin, N. H.: An Unusual Metastatic Manifestation of Hodgkin's Granuloma, Am. J. Roentgenol. **14**:251, 1925.

Rordorf, R.: Observations Regarding Nine Cases of Lymphogranuloma Malignum, Gior. ital. di mal. esot. e trop. **3**:234, 272, 301 and 328, 1930.

Saupe, E.: Bone Changes in Lymphogranulomatosis, Röntgenpraxis **2**:397, 1930.

Schinz, H. R., and Uehlinger, E.: Diagnosis, Differential Diagnosis, Prognosis and Therapy of the Primary Tumors and Cysts of the Skeletal System, Ergebn. de med. Strahlenforsch. **5**:470, 1931.

Simonds, J. P.: Hodgkin's Disease, Arch. Path. **1**:394 (March) 1926.

Symmers, D.: The Clinical Significance of the Pathological Changes in Hodgkin's Disease, Am. J. M. Sc. **167**:157 and 313, 1924.

Tetzner, E.: Lymphogranulomatosis in the Spinal Column, Frankfurt. Ztschr. f. Path. **42**:545, 1931-1932.

Uehlinger, E.: Lymphogranulomatosis of the Bones, in Schinz, H. R.; Baensch, W., and Friedl, E.: Lehrbuch der Röntgendiagnostik, mit besonderer Berücksichtigung der Chirurgie, Leipzig, Georg Thieme, 1932, vol. 1, p. 222.

On Bone Lymphogranulomatosis, Virchows Arch. f. path. Anat. **288**:36, 1933.

von Müllern, K., and Grossmann, B.: Contributions to the Knowledge of Primary Diseases of the Hematopoietic Organs, Beitr. z. path. Anat. u. z. allg. Path. **52**:276, 1912.

Voorhoeve, N.: Malignant Lymphogranulomatosis, Acta radiol. **4**:567, 1925.

Weber, F. P.: Paraplegia and Cauda Equina, Symptoms in Lymphogranulomatosis Maligna (Hodgkin's Disease), Quart. J. Med. **17**:1, 1923-1924.

Worster-Drought, C., and Hill, T. R.: Hodgkin's Disease, Proc. Roy. Soc. Med. **24**:282, 1931.

Ziegler: Hodgkin's Disease, Jena, Gustav Fischer, 1911.

A CLEAN INTESTINAL ANASTOMOSIS

AN EXPERIMENTAL STUDY

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The question of intestinal anastomosis has been attacked by numerous workers, and a tremendous literature has accumulated. Among the more recent workers, Halsted [1] published a paper in 1922 describing his blind-end circular suture, which acted as a great stimulus to investigations pertaining to the technic of intestinal suture. In 1922 Horine [2] stated that 217 methods had been suggested for performing intestinal anastomoses. Since his review, 58 additional publications bring the total to 275 proposals.

Naturally there are many duplications, and in general the suggested technics or methods can be classified under two main heads: the open method and the closed method. The stimulus for much of the work has been to find a so-called aseptic technic. Strict asepsis, from the surgical point of view, probably cannot be attained consistently. Technics affording a minimum of soiling have been devised, but there are factors other than contamination governing success or failure. An important and obvious factor is the size of the stoma at the site of anastomosis immediately after the operation as well as during the months to follow. The fear of temporary obstruction following the end-to-end anastomosis prevents its more frequent application. Much of the immediate obstruction is due to edema of a traumatized, inverted cuff at the line of suture. In the following procedure a minimum amount of tissue is inverted without crushing and without impairment of circulation.

PROCEDURE

The course of the operation is readily followed from the diagrams, supplemented by a few details as to the successive steps. The segment of bowel to be removed is freed, the mesentery is divided and unshod and noncrushing, intestinal clamps

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From the Laboratory of Experimental Surgery, Department of Surgery, Stanford University School of Medicine.

1. Halsted, W. S.: Blind-End Circular Suture of the Intestine, Ann. Surg. **75**:356, 1922.

2. Horine, C. F.: Aseptic Technic for the Resection of the Intestine, Ann. Surg. **76**:745, 1922.

are placed across the viscus (fig. 1). The bowel is divided with a cautery between the clamps, leaving about 0.5 cm. beyond each clamp so as to prevent the intestine from slipping out of the loose blades. After placing a purse-string suture of linen about 2 mm. from the edge of each clamp as indicated in figure 1*B*, the first posterior row of half-mattress sutures of fine black silk are introduced as close to the purse-string sutures as possible. Care must be taken to place all sutures in the same order, i.e., to begin each suture by taking a bite to include the submucosa, so that the exit of the needle from the wall of the bowel will be nearer the mesenteric border than its entrance, while the subsequent bite in the opposite section

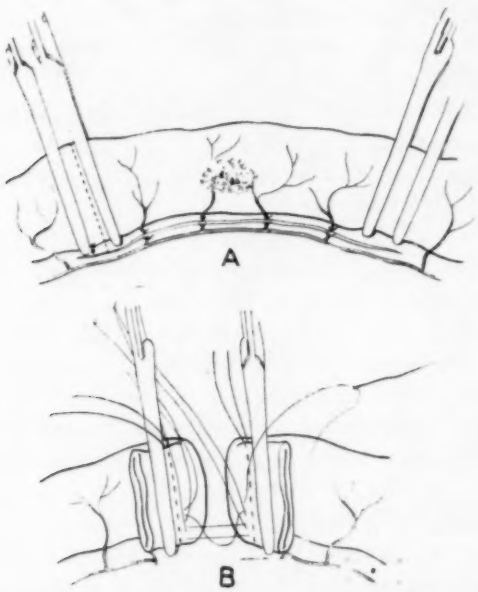

Fig. 1.—*A*, a segment of the bowel with the intestinal clamps in place for the division of the viscus with a hot cautery; *B*, the divided bowel with the two linen purse-string sutures placed and the first posterior row of anastomosing sutures being introduced.

of the viscus will be taken in the reverse order, so that the exit of the needle will be distal and its entrance proximal to the mesenteric border of the intestine. This is readily followed by tracing out the course of a single suture in figure 1*B*. If this precaution is not observed in placing the sutures, difficulties will be met in approximating the edges later. The ends of these sutures are tied together and placed in safety-pins, which in turn are threaded onto another pin as illustrated in figure 2. When the sutures are secured by the safety-pins, it is impossible to tangle them. In introducing the first anterior row of sutures, one begins at the mesenteric border of the intestine and observes the same precautions in placing them as in the case of the posterior row. In addition, the thread bridging between the two segments of bowel is carried around the ends of the occluding clamps as shown in figure 3.

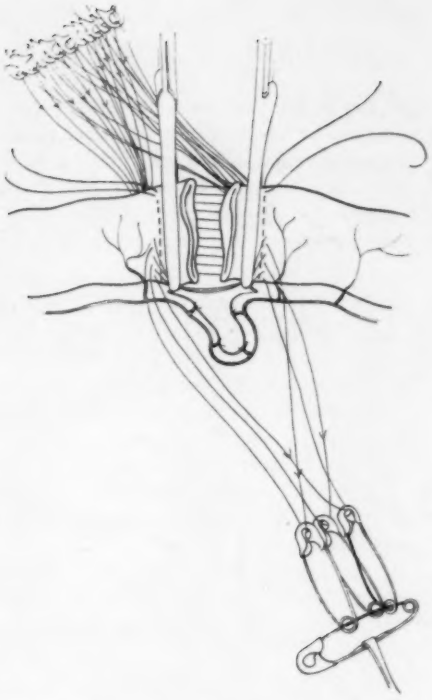

Fig. 2.—The first posterior row of sutures in place and the introduction of the first anterior row of anastomosing sutures; all of the anastomosing sutures are secured in safety-pins.

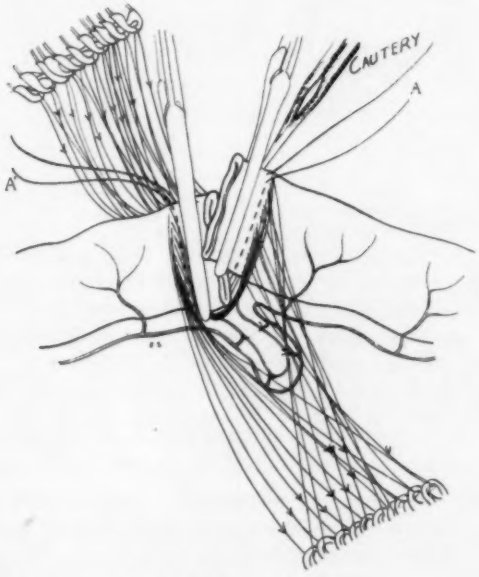

Fig. 3.—All of the first row of anastomosing sutures are in place, the bowel is lifted by the intestinal clamp and the area between the clamp and the purse-string suture *A* is cleared, ready for the removal of the intestinal cuff beyond the clamp. The edge of the clamp acts as a guide for the hot cautery.

With completion of the entire first row of sutures, the operator raises the end of one segment of bowel by grasping the intestinal clamp and smooths down the sutures with physiologic solution of sodium chloride, so that they will not lie in the area between the linen purse-string suture and the intestinal clamp but will rather "umbrella" down the sides of the intestine. This precaution is taken so as not to damage these structures in the subsequent division of the bowel. The

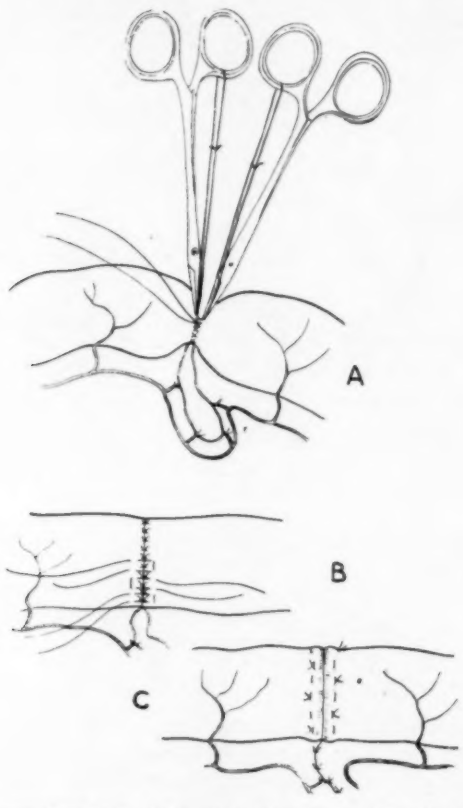

Fig. 4.—The approximation of the ends after removing the intestinal cuffs and pulling up the anastomosing sutures: *A,* all of the sutures of the first row are tied except the final ones before cutting the purse-string sutures against the jaws of the securing mosquito clamps; *B,* the first row is completed, and the purse-string sutures are released with the opening of the lumen of the bowel and the introduction of a second row of sutures; *C,* an illustration of the complete anastomosis, using the Halsted mattress suture in the second row of anastomosing sutures.

cuff of bowel beyond the purse-string sutures is to be resected by division of the bowel with a hot cautery against the clamp and beyond the purse-string sutures. After placing a first knot in the purse-string suture, an assistant pulls the suture taut at an angle of approximately 45 degrees with the intestinal clamp, so as not

to come in contact with the hot cautery, as the bowel is closed simultaneously with its division. The cautery is directed across the bowel against the jaws of the intestinal clamp, which thus determines the line of section and insures against damage to the sutures. The purse-string sutures are pulled up just tight enough to prevent leakage from the lumen of the bowel, but not enough to interfere with free bleeding from the larger vessels in the visceral wall. These vessels are clamped with small Halsted clamps and tied with fine silk. Usually three bleeding vessels will be found: two in the proximal segment and one in the distal segment of the bowel. Without placing a second knot in the purse-string sutures, they are secured with small Halsted clamps as illustrated in figure 4*A*.

The cauterized ends are approximated, the intervening slack in the anastomosing sutures is taken up by pulling each suture individually, and all but two of the sutures are tied. Then the purse-string sutures are cut close to the jaws of the securing clamps, the clamps are removed and the remaining two anastomosing sutures are tied. The bowel will remain constricted until massaged or forced open with axial pressure, when it will open out to its normal diameter. A second row can be laid down, using either a Halsted mattress suture, as shown in figure 4*B*, or a continuous Cushing stitch, as the operator chooses.

Obviously this technic can be applied to end-to-side and side-to-side anastomoses. This has been done readily and without other than self-evident modifications. It might be worth while to mention that no leakage occurs when the bowel is distended markedly with water after completion of the first line of sutures.

RESULTS

Once the entire technic was established, no deaths which could be attributed to the method occurred in forty-five successive operations. One animal died on the fifth postoperative day and showed bilateral pneumonia, one died on the ninth day of distemper, and another animal was killed by other dogs on the twelfth postoperative day. None of these animals had peritonitis, and the line of anastomosis showed normal healing. A stitch abscess was found in one animal killed on the tenth day following a second anastomosis done on the sigmoid flexure of the same animal ten days after the first operation.

Three series of twelve operations each were carried out on the sigmoid flexure: (1) first row, interrupted half-mattress sutures of fine black silk; second row, Halsted mattress sutures of fine silk; (2) first row, interrupted half-mattress sutures of fine black silk; second row, continuous sutures of fine black silk; (3) a single row of Halsted mattress sutures of fine black silk, placed after the ends of the bowel had been divided and closed by the purse-string sutures. In each series, specimens were taken immediately, six, twelve and twenty-four hours and two, three, five, seven, ten, fifteen, twenty and twenty-five days following the operation, and the condition of the abdominal cavity and stoma of the viscus was noted.

Whether or not the lumen of the bowel was patent was determined in the following manner: The gas in the bowel on one side of the anastomosis was milked out, and if the bowel was immediately refilled

by gas from the loop of viscera across the line of anastomosis, the lumen was considered patent. These conditions were fulfilled in all cases except three in the third series in which a single row of Halsted mattress sutures was placed after the ends of the bowels were closed with the purse-string sutures. In this series the bowel was found to be occluded on the third, fifth and seventh days. Opening of the bowel showed the lumen to be occluded by the edematous inverted shelf. Naturally, it would have been possible to bring about the same conditions in the other two series by turning in large amounts of tissue when placing the second row of sutures. But, as will be indicated later, the

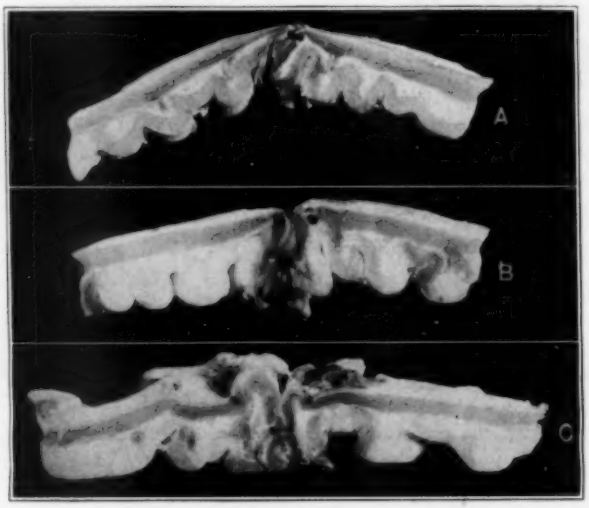

Fig. 5.—Sections taken immediately following the suture (all from the same segment of bowel): *A*, a cross-section with the first row of sutures placed; *B*, same as *A*, plus a second row of continuous sutures; *C*, same as *A*, plus a second row, using the Halsted mattress suture.

shelf is determined by the amount of tissue turned in with the second row of sutures and is under the absolute control of the operator.

Subsequently, in another series of experiments, nine end-to-end anastomoses were done on the small bowel using the technic employed in series 1 with consistently good results.

Practically all of the publications following the communication of Halsted [1] dealt with various methods of releasing the purse-string sutures of the blind ends so as to remove the diaphragm. No contributions were made which would lead to reduction in the amount of inverted viscus or to more accurate placing of the anastomosing sutures. In all

cases except Holman's [3] "presection" method the purse-string suture was tied down before the bowel was divided, or before the anastomosing sutures were placed. In the technic presented here, the anastomosing sutures are accurately placed directly against the purse-string sutures and not more than 2 mm. from the inverted end of the bowel. Furthermore, the sutures are placed while the bowel is held between clamps, so that corresponding portions of the bowel's cross-section are readily and accurately approximated.

No crushing clamps are applied to the intestine, so the opportunity for soiling by squeezing organisms through the visceral wall is mini-

Fig. 6.—Two specimens removed four months after anastomosis in the sigmoid flexure.

mized. The 2 mm. or less of inverted cuff has not been crushed and should show but slight trauma or devitalization. The operation recommended by Parker and Kerr,[4] using the "basting stitch," turns in a crushed and traumatized cuff of bowel, whereas, if the procedure described here is followed, there is no palpable thickening at the line of anastomosis when the lumen of the bowel is reestablished following the completion of the first row of sutures (fig. 5 *A*). Therefore a second row of sutures may be applied. And it is not necessary to limit the sutures to the smallest possible bites. They are rather placed so as

3. Holman, Emile: End-to-End Anastomosis of the Intestine by Presection Sutures, Bull. Johns Hopkins Hosp. **31**:300, 1920.

4. Parker, E. M., and Kerr, H. H.: Intestinal Anastomosis Without Open Incision by Means of Basting Stitches, Bull. Johns Hopkins Hosp. **19**:132, 1908.

to turn in the amount of lumen which will provide the extent of approximation of the serosa desired by the operator (fig. 5). For all practical considerations the shelf at the line of anastomosis depends on the tissue turned in by the second row of sutures, and this is under the direct control of the surgeon.

Obviously, this procedure can be interrupted at any stage by dividing the bowel, tying the purse-string sutures and performing an enterostomy. Also, it is noteworthy that from the time the intestinal clamps are placed until after completion of the entire first row of sutures the viscera need not be handled directly. So long as the intestinal clamps are in place, the bowel can be manipulated from the handles of these instruments. After they have been removed, the Halsted clamps on the purse-string sutures may be used to approximate the blind ends.

The method has the disadvantages of any technic employing interrupted sutures in that it requires more time than is necessary when continuous sutures are used, but experience shows that it requires no more time than any other method in which interrupted sutures are used. The maze of untied sutures (fig. 3) must appear hopeless at first glance, but if they are handled as outlined and placed on safety-pins, no difficulties will be encountered. This method of dealing with numerous untied sutures should find application in other procedures in which the same conditions are met.

SUMMARY

1. A clean technic is described for closed intestinal anastomosis in which the trauma and soiling are reduced to a minimum and the amount of inverted cuff is under the direct control of the operator.

2. A method for handling many untied sutures is suggested.

3. A novel procedure is given for the simultaneous division and occlusion of the bowel between the clamp and purse-string suture.

4. The results of forty-five experimental operations are reviewed.

PATHOLOGIC FRACTURES OF THE SPINE ASSOCIATED WITH DISORDERS OF CALCIUM METABOLISM

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The occasional report in the literature of pathologic fractures of the spine as a result of the loss of calcium associated with tumor of the parathyroid glands seems to have given rise to the impression that this is a rare and strange condition. It is my purpose to point out that pathologic fractures resulting from the loss of calcium from the spinal column are not uncommon and are, in the majority of cases, due to a faulty diet. In a previous article,[1] six cases were analyzed to determine the changes in the intervertebral disk associated with this condition. In four of these six cases the condition was due to faulty diet. I shall present in outline four additional cases and a description of this condition as a definite clinical entity.

CLINICAL OBSERVATIONS

The typical clinical course starts with fatigue referred to the spine, usually with some accentuation of the anteroposterior curves. This condition increases in severity, and usually before the patient consults an orthopedic surgeon he has subjected the spine to sudden strain. This is followed by a sharp pain localized in its greatest intensity and usually accompanied by pains radiating along the spinal nerve roots, indicating that a fracture has taken place. In one of the cases presented, this pain occurred when the patient stooped over to pick an object off the floor. In the most severe case, one of those included in the aforementioned article,[1] the patient sustained additional fractures from simply turning in bed. On examination there is tenderness throughout the affected portions of the spine over the spinous processes. Even when no fracture has occurred, the diagnosis rests on roentgenographic observations, which are described in later paragraphs.

Age.—The age of the patient at the time of the onset apparently is not a factor in this condition. The youngest patient was 18, and the oldest, 68 years of age.

Read at the clinical conference of the orthopedic section of the Post-Graduate Medical School of Columbia University, April 13, 1933.

1. Moffat, Barclay W.: Enlargement of the Intervertebral Disc Associated with Decalcification of the Vertebral Body: A Compensatory Hypertrophy, J. Bone & Joint Surg. **15**:679 (July) 1933.

Etiology.—The etiologic factor is necessarily a condition in which either the normal amount of calcium is not taken from the intestinal tract or an abnormal amount is being excreted. The skeleton is the storing place of calcium in the body, and that contained in the spinal column seems to be more mobile than that stored in other bones. That this is the case appears likely when one considers the cancellous structure of the vertebral body and its rich supply of blood. In only one instance did roentgen examination show the rest of the skeleton to be deficient in calcium.

Considering the first of the two causes: There may be either an insufficient calcium content in the food or a local condition in the intestinal tract interfering with the passage of calcium through the intestinal wall. In regard to the quantity of calcium in the food, it should be pointed out that this nation as a whole subsists on the absolute minimum intake of calcium compatible with health. It is not surprising, therefore, that the diet drops below this minimum in a great number of persons. The second factor concerning the intake of calcium includes an alkaline condition in the intestinal tract causing the formation of insoluble salts and the presence of fatty acids which bring about the saponification of calcium with consequent excretion of these insoluble materials. A lack of vitamin D also inhibits passage of calcium into the circulation.

In by far the greater proportion of cases the fault lies in the intake of calcium. In cases of abnormal excretion of calcium, the endocrine glands are most often at fault. The parathyroid glands regulate the output of calcium, that is, hyperactivity of a parathyroid gland results in an outpouring of calcium from the skeleton by way of the alimentary and urinary tracts. Though the fact is not yet generally recognized, the pituitary gland is also concerned with the metabolism of calcium. A tumor of either the pituitary or a parathyroid gland, therefore, may result in the condition which I describe.

Roentgenographic Observations.—The roentgenographic observations are characteristic. In the earlier cases it is not always possible to demonstrate the presence of osteoporosis, inasmuch as the density of the spinal shadow in the x-ray picture may vary with the differing thicknesses of the patient's body and with the technic of the roentgenologist. The earliest constant sign is a change in the shape of the intervertebral disk, which takes on a more pronounced biconcave form and at times becomes completely spherical. This is due to hypertrophy, as shown in the article to which I have referred.[1]

The rapidity of the onset may also be judged by the presence or absence of condensation of bone at the upper and lower margins of the vertebral body. When the condition is slowly progressive, the white line will be apparent, indicating that the body has had time to strengthen its wall against the pressure of the hypertrophied disk. The process

is similar to that which occurs in smaller areas of the margins of the body in the case of extravasation of the contents of the nucleus pulposus, in which the same line of condensed bone is found at the bottom of an indentation, marking the site of the break in the envelop of the nucleus.

Fractures, when they occur, are compression fractures, and it is characteristic that they are not accompanied by extravasation of the contents of the disk with a consequent lessening of its height, as are

Fig. 1.—Roentgenogram of the spine in a case of loss of calcium; an early stage of the process is shown.

fractures occurring in normal vertebral bodies in which the trauma is necessarily greater.

REPORT OF CASES

CASE 1.—R. R., a woman, aged 27, complained of fatigue in the back without cause in March, 1932. This became worse. In February, 1933, she experienced a sudden sharp pain in the lower dorsal region while performing an exercise which consisted of touching the floor with her legs which were extended above her head while she was lying in the supine position. The pain radiated about the trunk following the course of the spinal nerve roots. A roentgenogram (fig. 1) was taken

on March 18, 1933, and shows osteoporosis of the bodies, slight increase in the height of the intervertebral disks and condensation of bone at the upper and lower margins of the bodies. There is a compression fracture of the tenth dorsal vertebra with slight angulation of the spine at this portion. The condition is in an early stage and of slow onset.

CASE 2.—L. L., a woman, aged 68, complained of fatigue in the back over a period of years previous to my seeing her, which she ascribed to age and for which she did not seek treatment until, in stooping to pick an article from the floor, she experienced a snapping sensation in the back accompanied by severe pain

Fig. 2.—Roentgenogram of the spine in a case of loss of calcium in which the changes are more advanced.

and collapse. The roentgenogram (fig. 2) shows the same condition as in the previous case but in a more advanced state. The biconcave appearance of the disks, the osteoporosis and the condensation of the margins are more marked. There is a compression fracture of the twelfth dorsal and first lumbar vertebrae.

Determination of the Calcium Balance.—The calcium balance indicated dietary deficiency. The daily diet supplied 0.558 Gm. of calcium. The amounts of calcium excreted in the urine were as follows: July 18 (volume of urine, 645 cc.), 0.227 Gm.; July 20 (volume, 785 cc.), 0.283 Gm.; July 23 (volume, 600 cc.), 0.190 Gm.

From July 18 to July 20 the feces (moist weight, 150 Gm.; dry, 24.6 Gm.) contained 0.542 Gm. of calcium. The total intake of calcium for July 18 and 19 was 1.116 Gm.; the total amount excreted was 1.010 Gm.; the gain in calcium was 0.106 Gm.

On July 21, the feces (moist, 395 Gm.; dry, 42 Gm.) contained 0.427 Gm. of calcium. The total intake of calcium was 0.558 Gm.; the total amount excreted was 0.661 Gm.; the loss in calcium was 0.103 Gm.

On July 22, the feces (moist, 380 Gm.; dry, 27 Gm.) contained 0.589 Gm. of calcium. The total intake of calcium was 0.558 Gm.; the total amount excreted was 0.823 Gm.; the loss in calcium was 0.265 Gm.

Fig. 3.—Roentgenogram of the spine showing a compression fracture of the twelfth dorsal vertebra.

On July 23, the feces (moist, 445 Gm.; dry, 26 Gm.) contained 0.154 Gm. of calcium. The total intake of calcium was 0.558 Gm.; the total amount excreted was 0.344 Gm.; the gain in calcium was 0.214 Gm.

On July 20, the blood calcium was 11.4 Gm. and the blood phosphorus 3 mg. per hundred cubic centimeters.

CASE 3.—H. W., a woman, aged 59, complained of fatigue in the back over a period of four years, with marked increase in local pain following a fall. A roentgenogram (fig. 3) taken in March, 1932, shows the same condition as in the previous cases with compression fracture of the twelfth dorsal vertebra.

CASE 4.—C. F., a woman, aged 48, complained of fatigue in the back over a period of several months. There was an onset of sharp pain following an attempt to lift a patient out of bed. The roentgenogram (fig. 4) shows the same condition as in the previous cases with compression fracture of the ninth and twelfth dorsal vertebrae.

Determination of Calcium and Phosphorus Balances.—The calcium and phosphorous balances indicated dietary deficiency. The daily diet was varied. On July 29, 1932, the report on the feces was: total weight, 35 Gm.; moisture, 73 per cent; dry weight, 9.5 Gm.; calcium, as Ca, 0.160 Gm.; phosphorus, as P, 0.061 Gm.

Fig. 4.—Roentgenogram of the spine showing compression fractures of the ninth and twelfth dorsal vertebrae.

The report on the urine was: volume, 1,200 cc.; calcium, as Ca, 0.028 Gm.; phosphorus, as P, 0.105 Gm. The intake of calcium in the diet was 0.535 Gm.; that of phosphorus, 0.943 Gm. The gain in calcium was 0.347 Gm.; in phosphorus, 0.777 Gm.

On July 30, the report on the feces was that there had been none. That on the urine was as follows: volume, 1,480 cc.; calcium, as Ca, 0.028 Gm.; phosphorus, as P, 0.878 Gm. The intake of calcium in the diet was 0.556 Gm.; that of phosphorus, 1.235 Gm. The gain in calcium was 0.528 Gm.; in phosphorus, 0.357 Gm.

On July 31, the report on the feces was: total weight, 1,100 Gm.; moisture, 94.3 per cent; dry weight, 62.7 Gm.; calcium, as Ca, 0.546 Gm.; phosphorus, as

P, 1.826 Gm. The report on the urine was: volume, 700 cc.; calcium, as Ca, 0.065 Gm.; phosphorus, as P, 0.372 Gm. The intake of calcium in the diet was 0.554 Gm.; that of phosphorus, 1.230 Gm. The loss in calcium was 0.057 Gm.; in phosphorus, 0.968 Gm.

On August 1, the report on the feces was: total weight, 40 Gm.; moisture, 76 per cent; dry weight, 9.6 Gm.; calcium, as Ca, 0.150 Gm.; phosphorus, as P, 0.077 Gm. The report on the urine was: volume, 1,400 cc.; calcium, as Ca, 0.051 Gm.; phosphorus, as P, 0.826 Gm. The intake of calcium in the diet was 0.550 Gm.; that of phosphorus, 1.215 Gm. The gain in calcium was 0.349 Gm.; in phosphorus, 0.312 Gm.

TREATMENT

The first requisite is, of course, the determination of the causes in the particular case. Evidences of pituitary disorder should be searched for, and the sugar tolerance test should be carried out. Parathyroid disorder may sometimes be diagnosed only by elimination of other possible factors, though in some cases a palpable tumor of one of these glands is present. The calcium and phosphorous balances should be worked out to eliminate the alimentary factor. In the case of tumor of a parathyroid gland, the treatment is necessarily removal of the gland. In the case of alimentary deficiency the patient should be given calcium gluconate and increasing doses of viosterol. The back should be supported with a brace rather than with a plaster cast, and the patient should be kept out of bed. The reason for these measures is, of course, to prevent further loss of calcium from disuse.

CONCLUSIONS

1. Loss of calcium from the spinal column presents a definite clinical picture.

2. This condition may be diagnosed and a prognosis given by definite roentgenographic signs in the early stages, when the process may be easily checked.

3. Pathologic fractures commonly result in the later stages.

4. In the majority of cases the diet is at fault, and only rarely is the faulty metabolism of calcium due to tumor of the pituitary or parathyroid glands.

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TOXEMIA IN ACUTE INTESTINAL OBSTRUCTION

TOXICITY OF INTESTINAL CONTENTS, WITH SPECIAL REFERENCE TO THE PANCREATICODUODENAL SECRETION

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In general, the experimental studies on the causes of death in acute intestinal obstruction have resulted in a tangle of conflicting opinions. The work of Haden and Orr [1] on the significance of chemical changes in the blood threw a new light on the problem, and this led to a series of investigations [2] which in part offer an explanation for the lack of agreement in previous experimental work. It is now generally conceded that the issue is clarified by a recognition of two fundamental types of intestinal obstruction: (1) simple obstruction and (2) strangulation. In simple intestinal obstruction in which there is no interference with the circulation of the intestinal wall, the chief cause of death is the metabolic disturbance resulting from the loss of fluids and electrolytes. Obstruction, however, is practically always complicated by damage to the intestine from overdistention or strangulation. Although the importance of dehydration and alkalosis must always be considered, there are other factors even more important. Frequently gangrene of the bowel and peritonitis are grossly apparent causes of death. In many cases of obstruction, however, the death seems inexplainable, except on the basis of some undetermined factor which is assumed to be a specific toxemia.

The toxic substances which may be demonstrated in the contents of an obstructed bowel have been studied repeatedly. Much significance has been attached to the symptoms produced by injecting into animals the contents of obstructed intestinal loops. It has been assumed that

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From the Research Division, Indiana University School of Medicine; the Eli Lily Research Fellowship.

1. Haden, R. L., and Orr, T. G.: Chemical Changes in the Blood of the Dog After Intestinal Obstruction, J. Exper. Med. **37**:365 (March) 1923; The Effect of Sodium Chloride on the Chemical Changes in the Blood of the Dog after Pyloric and Intestinal Obstruction, ibid. **38**:55 (July) 1923.

2. Gatch, W. D.; Trusler, H. M., and Ayres, K. D.: Acute Intestinal Obstruction Mechanism and Significance of Hypochloremia and Other Blood Chemical Changes, Am. J. M. Sc. **173**:649 (May) 1927.

these experiments constitute evidence concerning toxemia in intestinal obstruction; it has been assumed that the normal intestinal contents is for the most part innocuous,[3] and that a specific toxin is formed primarily as the result of obstruction. Here again, however, results and conclusions are controversial. We are reporting a series of investigations on this subject.

In this article it is our purpose to present the results of numerous tests on the toxicity of the contents of normal as well as obstructed intestine. We have collected the material from human subjects as well as from experimental animals. Many experiments of this type have been reported previously by other workers using various methods of investigation. Cooper [4] gave a complete bibliography of this work and elaborated on the extreme diversity of opinion concerning the toxicity of intestinal contents. It is obvious that results will vary according to the manner of preparing and testing such material, and this explains much of the controversy.

METHOD OF TESTING

This report includes only the results obtained by testing the material either in its crude state or modified by such simple procedures as centrifugation, filtering or autoclaving in preparation for intravenous injection. The criteria of toxicity we used are likewise simple. The tests include: (1) intravenous and intraperitoneal injection of the various preparations into dogs, rabbits and mice with observation as to death or toxic symptoms in the animals, and (2) kymographic record of the effects produced on the blood pressure by such injections into dogs under ether anesthesia.

The second method of study was particularly valuable in making comparative examinations of numerous samples. It also gave us information concerning the toxicity of many preparations difficult to evaluate by gross observation following their injection into normal animals. The dosage of the injection for dogs and rabbits varied from 1 cc. for each 5 Kg. to 5 cc. per kilogram of body weight. The small injections of 0.2 cc. per kilogram were extremely valuable in kymographic studies comparing the effects of various samples of material in the same animal. We found that in this dose preparations possessing any significant toxicity caused a sharp fall in blood pressure with a prompt return to normal. The injection was made at a uniformly rapid rate (approximately 0.5 cc. per second). With an extremely slow injection the response was less definite.

By such observations we can expect to demonstrate only the presence or absence of toxic substances. A study as to the possibilities of their

3. Ellis, J. W.: Cause of Death in High Intestinal Obstruction, Ann. Surg. **75**:429 (April) 1922.

4. Cooper, H. S. F.: The Cause of Death in High Obstruction, Arch. Surg. **17**:918 (Dec.) 1928.

absorption through the intestinal wall is being published separately. Further information obtained by chemical analysis also follows as a subsequent publication. As a basis for the discussion which follows we have made hundreds of tests. It is our aim to present sufficient data to demonstrate the facts. To display the entire investigation in detail is futile and unnecessary.

TOXICITY OF NORMAL INTESTINAL CONTENT

The normal contents of the bowel in dogs and in human subjects is always toxic when injected intravenously into animals. We wish to emphasize this fact because previous reports on the subject have seemed to conflict and have caused confusion. Davis and Stone [5] and also Dragstedt and his co-workers [6] reported the normal secretion of the intestinal mucosa to be innocuous when so collected as to be free from other substances. We confirmed this observation and have no reason to doubt it. The normal contents of the bowel, however, is an entirely different material and, even in the absence of food, will include gastric juice, bile and pancreatic juice in addition to the normal secretion of the intestinal mucosa. Nevertheless, the terms have been confused, and there is a widespread impression that the normal intestinal contents has little or no toxicity and becomes toxic directly only as the result of obstruction. This conception is a fallacy. It is true that marked changes occur in the intestinal contents as the result of obstruction, and these will be discussed later. In regard to the demonstration of toxic substances, however, our tests consistently showed the normal intestinal contents to be even more toxic than material removed from an obstructed bowel. We tested numerous samples of material collected from both small and large intestines of normal dogs under various conditions of feeding or fasting, filtrates from human feces, material promptly removed from the human small intestine at autopsy and drainage material from enterostomy in man. Though obviously there must be considerable variation in the constituents of such material, practically all the samples showed toxic properties causing depression in the blood pressure. To rule out the known toxic effect of intravenously injecting large numbers of bacteria or gross particulate matter we used Berkefeld filtrates (diluting the original sample with saline solution when necessary). Also for comparison we studied the original liquid samples as nearly unchanged as possible, merely centrifugating and injecting the supernatant fluid through a needle of 22 gage or less.

5. Davis, D. M., and Stone, H. B.: Studies on the Development of Toxicity in Intestinal Secretion, J. Exper. Med. **26**:687 (Nov.) 1917.

6. Dragstedt, L. R.; Moorhead, J. J., and Burcky, F. W.: The Nature of the Toxemia of Intestinal Obstruction, Preliminary Report, Proc. Soc. Exper. Biol. & Med. **14**:17 (Oct.) 1916.

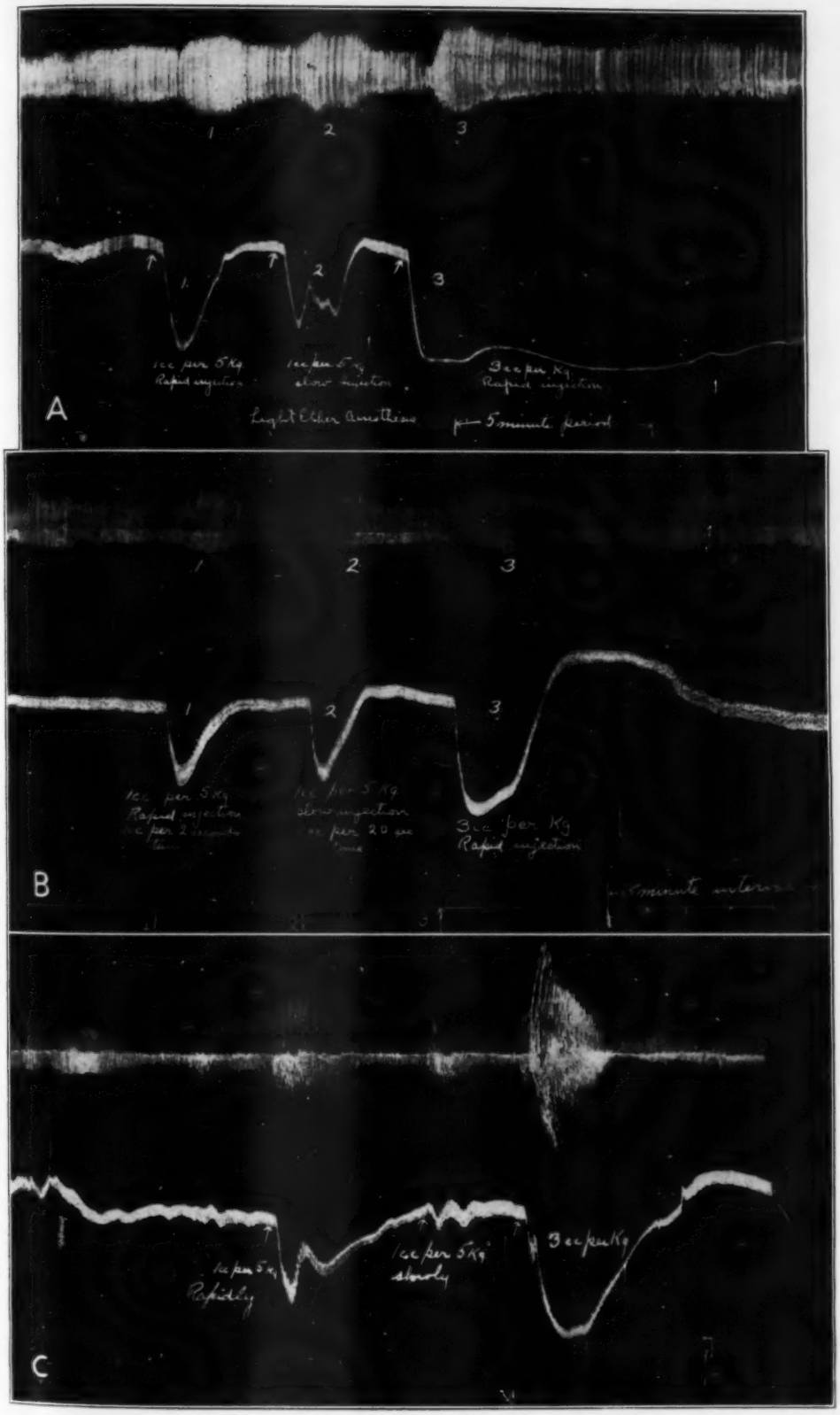

Fig. 1.—Kymograph series 1A, showing the toxicity of the normal contents of the small intestine of dogs on intravenous injection into a dog anesthetized with ether. The upper tracing shows the respirations; the lower, the blood pressure. The spaces between arrows indicate five minute periods. *A* was obtained following the injection of centrifugated supernatant fluid; *B*, following the injection of a Berkefeld filtrate; *C*, following the injection of autoclaved centrifugated supernatant fluid.

Tables 1 and 2 outline the results of such a series of tests. The toxic symptoms mentioned in all the tables are typically as follows: If the animal is a dog, the toxic injection is promptly followed by dyspnea, salivation, vomiting, defecation or tenesmus, micturition, muscular tremor and prostration. Following this severe reaction the animal

TABLE 1.—*Toxicity of Normal Contents of Small and Large Bowel in Dogs* *

Test Animal	Material Injected	Intravenous Dose†	Result
Dog 485	Sample 1; contents of small intestine of normal dog; centrifugated supernatant fluid	3 cc.	Severe toxic symptoms; died in 20 hours
Dog 481	Berkefeld filtrate of sample 1.....	3 cc.	Mild toxic symptom; recovered
Dog 497	Sample 2; contents of small intestine of normal dog; centrifugated supernatant fluid	3 cc.	Severe toxic symptoms; died in 7 hours
Dog 496	Berkefeld filtrate of sample 2.....	3 cc.	Toxic symptoms; died in 48 hours
Dog 488	Sample 3; contents of small intestine of normal dog; centrifugated supernatant fluid	3 cc.	Violent toxic symptoms; died in 30 min.
Dog 484	Berkefeld filtrate of sample 3.....	3 cc.	Toxic symptoms; recovered
Dog 575	Sample 4; contents of small intestine of normal dog; centrifugated supernatant fluid	3 cc.	Violent toxic symptoms; died in 2 hours
Dog 571	Berkefeld filtrate of sample 4.....	3 cc.	Died in 2 hours
Dog 573	Sample 4, autoclaved and centrifugated....	3 cc.	Died in 10 hours
Dog 648	Sample 5; contents of large bowel of normal dog; material suspended in equal part of saline solution; centrifugated supernatant fluid	3 cc.	Mild toxic symptoms; recovered
Dog 642	Berkefeld filtrate of sample 5.....	3 cc.	Mild symptoms; recovered
Dog 644	Sample 5, autoclaved and centrifugated....	3 cc.	Mild symptoms; lived 10 days
Rabbit 28	Sample 6; contents of small intestine of normal dog; centrifugated supernatant fluid	5 cc.	Convulsions; immediate death
Rabbit 29	Berkefeld filtrate of sample 6.....	5 cc.	Died in 18 hours
Rabbit 70	Sample 7; contents of small intestine of normal dog; centrifugated supernatant fluid	5 cc.	Convulsions; immediate death
Rabbit 71	Berkefeld filtrate of sample 7.....	5 cc.*	Convulsions; immediate death
Rabbit 23	Sample 8; contents of large bowel of normal dog; material suspended in equal part of saline solution; centrifugated supernatant fluid	5 cc.	Convulsions; immediate death
Rabbit 24	Berkefeld filtrate of sample 8.....	5 cc.	Recovered

* The term "normal" is used merely to indicate the absence of obstruction and ordinary conditions of feeding.
† Per kilogram of body weight.

usually dies in a few hours. If, however, the reaction is less drastic, as is often the case even with large doses, the dog frequently recovers completely. Rabbits behave in an entirely different manner. If the injection is extremely toxic, the rabbit promptly dies in convulsions. If death does not occur thus, the animal merely becomes prostrated and dies or recovers after a variable number of hours. Though rabbits are easily killed by injections containing particulate matter, they may tolerate in proportion to their weight even larger doses of Berkefeld filtrates than dogs do. The same is true of mice receiving intraperitoneal injections (doses of 1 and 2 cc.). These small animals would at first thought

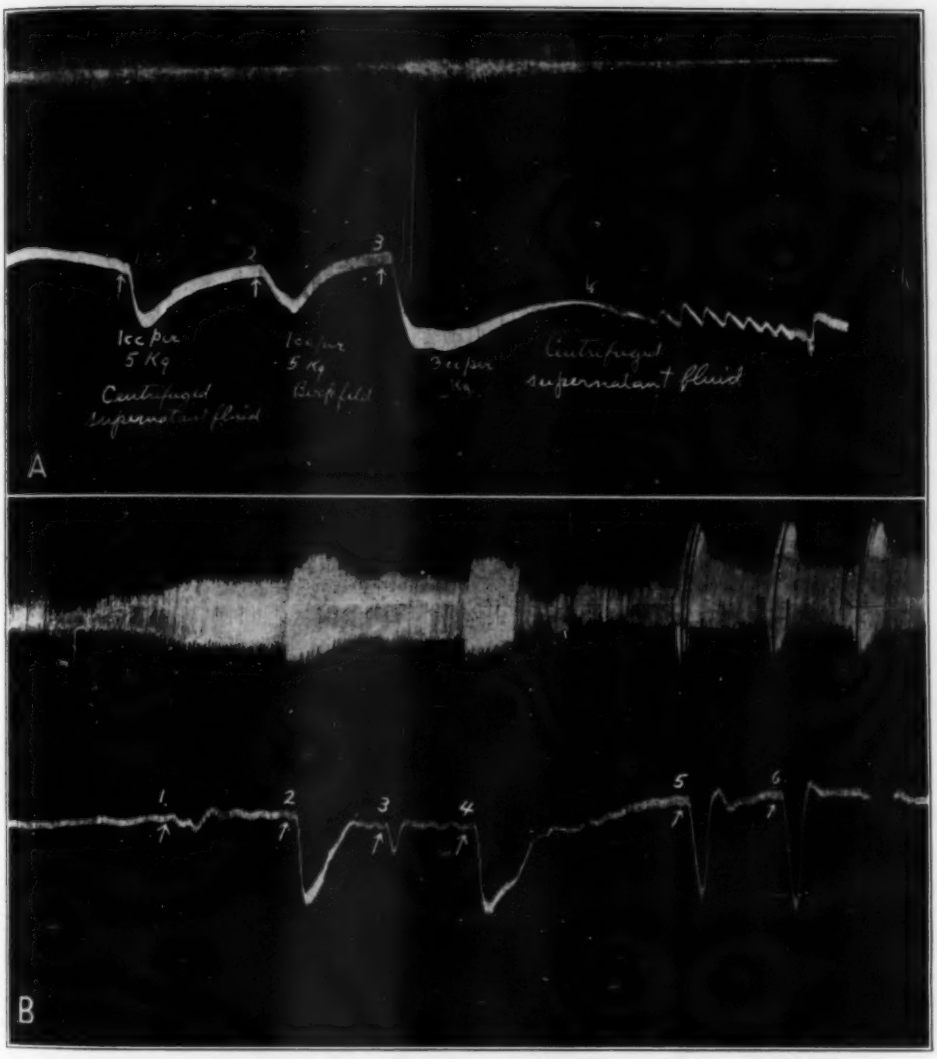

Fig. 2.—Kymograph series 1B, showing the results of tests on the normal content of the large intestine of dogs. The samples were suspended in equal parts of saline solution, and intravenous injections made into a dog anesthetized with ether. The spaces between the arrows indicate five minute periods. *A* was obtained following the injection of the normal contents of the large intestine of dogs. *B* shows the variation in toxicity of material from the large intestine of a dog as compared with the material from the small intestine of the same animal. All doses were 1 cc. for each 5 Kg. of body weight. The material injected was as follows: 1. Supernatant fluid, contents of large intestine, dog A; sample suspended in equal part of saline solution. 2. Supernatant fluid, undiluted contents of small intestine, dog A. 3. Sample from large bowel, dog B. 4. Sample from small bowel, dog B. 5. Sample from large bowel, dog C. 6. Sample from small bowel, dog C.

seem to be of value in detecting small amounts of these toxins. The few we have used have been so resistant as to offer little aid in this study. In general, we have not found intraperitoneal injection a satisfactory test. Though absorption by that route may often be sufficient to produce toxic symptoms or death in dogs, results are easily complicated by peritonitis when any of the more crude preparations are injected.

Of all the tests, the kymographic studies have been of greatest value. One might raise the objection that toxins could be present and yet

TABLE 2.—*Toxicity of Human Intestinal Contents in the Absence of Obstruction* *

Test Animal	Material Injected	Intravenous Dose†	Result
Dog 574	Sample 1; contents of human small intestine removed soon after death from apoplexy; centrifugated supernatant fluid	3 cc.	Violent toxic symptoms; died in 30 minutes
Dog 576	Berkefeld filtrate of sample 1.....	3 cc.	Toxic symptoms; recovered
Dog 572	Autoclaved and centrifugated portion of sample 1	3 cc.	Toxic symptoms; recovered
Rabbit 10	Sample 2; contents of human small intestine removed soon after death from pneumococcic peritonitis; centrifugated supernatant fluid	5 cc.	Convulsions; died at once
Rabbit 8	Berkefeld filtrate of sample 2.....	5 cc.	Died in 16 hours
Rabbit 11	Autoclaved and centrifugated portion of sample 2	5 cc.	Died in 16 hours
Dog 641	Sample 3; human feces suspended in equal parts of saline solution; centrifugated supernatant fluid	3 cc.	Toxic symptoms; died in 7 hours
Dog 640	Berkefeld filtrate of sample 3.....	3 cc.	Mild toxic symptoms; recovered
Dog 643	Autoclaved and centrifugated portion of sample 3	3 cc.	Mild toxic symptoms; recovered
Dog 293	Drainage from enterostomy of upper jejunum, case 1; centrifugated supernatant fluid	3 cc.	Severe toxic symptoms; died in 24 hours
Dog 344	Enterostomy drainage, case 1; Berkefeld filtrate	3 cc.	Died in 2 days
Dog 296	Enterostomy drainage, case 1; autoclaved and centrifugated supernatant fluid	3 cc.	Recovered
Rabbit 83	Enterostomy drainage, case 1; centrifugated supernatant fluid	5 cc.	Died in 3 days
Rabbit 63	Enterostomy drainage, case 1; Berkefeld filtrate	5 cc.	Lived 4 weeks
Rabbit 78	Enterostomy drainage, case 1; autoclaved and centrifugated supernatant fluid	5 cc.	Lived 3 weeks

* Samples obtained from fresh autopsy material, suspension of feces in saline solution and enterostomy drainage.

† Per kilogram of body weight.

not be detectable on the kymographic tracing. However, repeated comparisons have demonstrated that any sample of intestinal material capable of producing toxic symptoms tends proportionately to exert a surprisingly characteristic depressant action on the blood pressure.

Berkefeld filtrates of the normal intestinal contents are much less toxic than the centrifugated supernatant fluid. Autoclaved preparations are similarly reduced in toxicity. Kymographic studies, however, show all these preparations to possess, even in small doses, a powerful though transient depressing action on the blood pressure. The large doses give an effect which is more prolonged and may or may not permit complete return to normal.

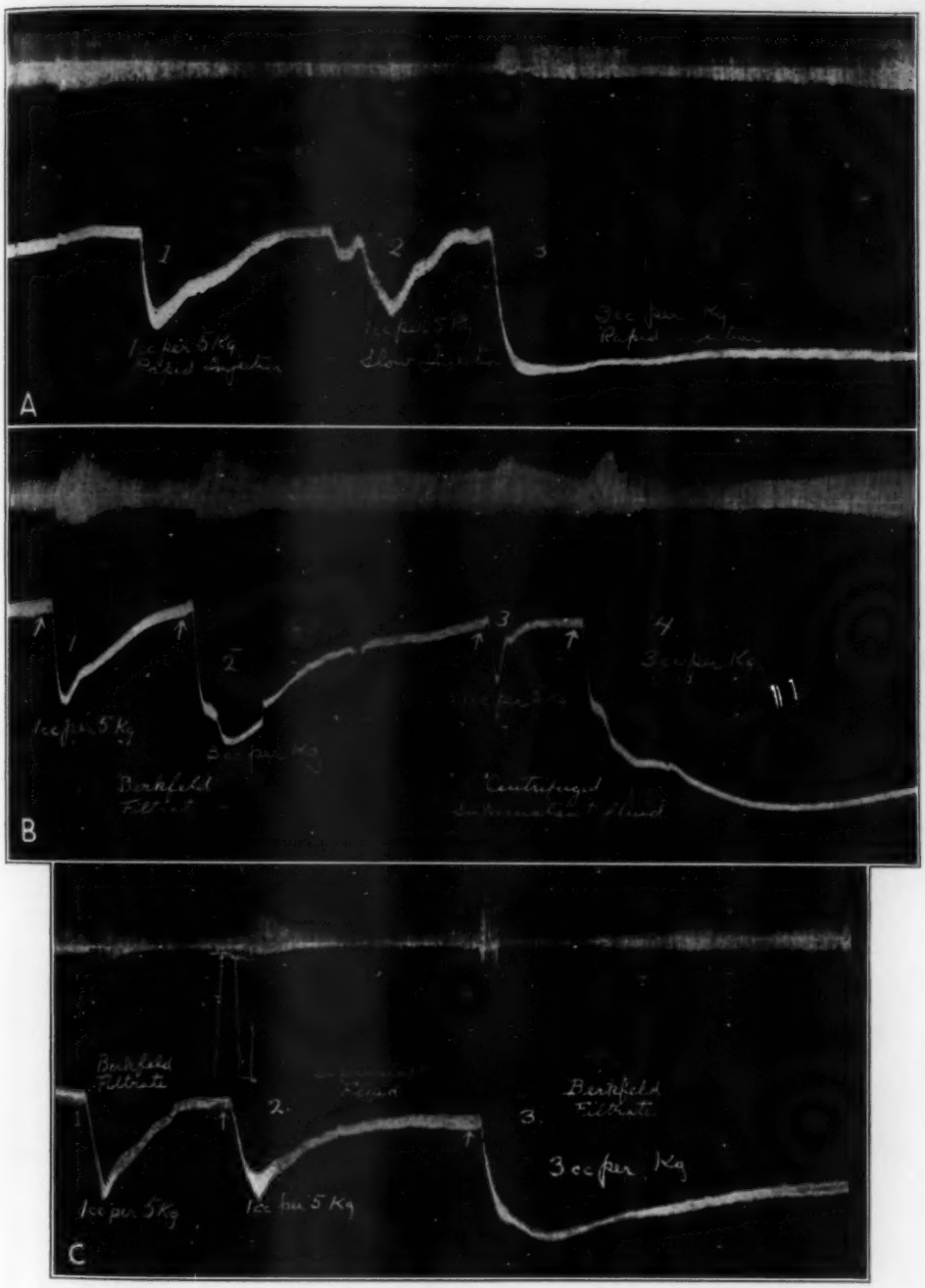

Fig. 3.—Kymograph series II, showing the results of tests on the normal contents of human intestine. Intravenous injections were given dogs under ether anesthesia. The upper tracings show the respirations; the lower, the blood pressure. The spaces between arrows indicate five minute periods. *A* was obtained following the injection of a Berkefeld filtrate of the normal contents of the small intestine (fresh autopsy specimen); *B*, following the injection of human feces suspended in saline solution (equal parts). *C* shows the toxicity of drainage material from a high enterostomy performed for relief of obstruction in a human subject.

Filtered suspensions of human feces and similar preparations of material from the large bowel of dogs are less toxic than material taken from the small intestine. At first thought this might be explained by the dilution necessary in making the liquid suspension of samples from the large bowel. One must admit, however, that the sample from the large bowel is a dehydrated residue of material formerly in liquid form in the small intestine.

Before discussing what possible significance these elementary facts may have in the study of intestinal obstruction, let us consider the sources of this toxic property. Products of protein degradation, bacterial toxins, bile or other digestive juices and all the heterogeneous products of digestion could be considered. Many of these and numerous other substances intravenously injected may cause a drop in the blood pressure and other symptoms similar to the reaction we have described. Further consideration of all these possibilities is unnecessary, however. The experiment outlined in table 3 demonstrates a salient fact.

TOXICITY OF THE PANCREATIC SECRETION

The pancreatic secretion as obtained from an isolated duodenal loop fistula is violently toxic when injected intravenously. The following experiment, one of several similarly performed, has enabled us to collect samples of material free from food, bile, gastric secretion and all other substances except pancreatic juice plus the secretions of the duodenal mucosa. This material is highly toxic when collected and tested fresh. Its toxicity is not materially altered by stagnation in the loop. Neither does it change appreciably on long standing in the refrigerator. The pancreatic juice alone as drained fresh from a cannula placed in the pancreatic duct likewise demonstrates a depressant action on the blood pressure. Though we have not completed our studies on this point, we have found thus far that the secretion so obtained is less toxic than the combined secretion of the pancreas and duodenum. In fact, samples collected from isolated duodenal loop fistulas possess toxicity equal to or greater than that of any material we have tested. Because of this observation we are impressed that any consideration of toxicity due to other products of digestion or bacterial putrefaction is of minor importance as concerns the study of normal intestinal contents. In the study of contents from obstructed bowel we must consider the various factors which modify the normal.

Protocol (Dog 264).—Food was withheld from a dog for forty-eight hours. Laparotomy was performed under ether anesthesia; the pylorus was sectioned and ligated and the stump inverted. The common bile duct was ligated and the gallbladder drained to the outside. The ligament of Treitz was divided sufficiently to permit a high gastrojejunostomy. The duodenum was sectioned just proximal to the gastrojejunostomy, and both stumps were inverted, the proximal duodenal

stump enclosing a short rubber tube which was brought through the abdominal wall. This tube drained freely the combined pancreaticoduodenal secretion. Tests on this material freshly collected were highly toxic as shown in kymograpic record III (fig. 4). Additional toxicity tests are shown in table 3. The animal

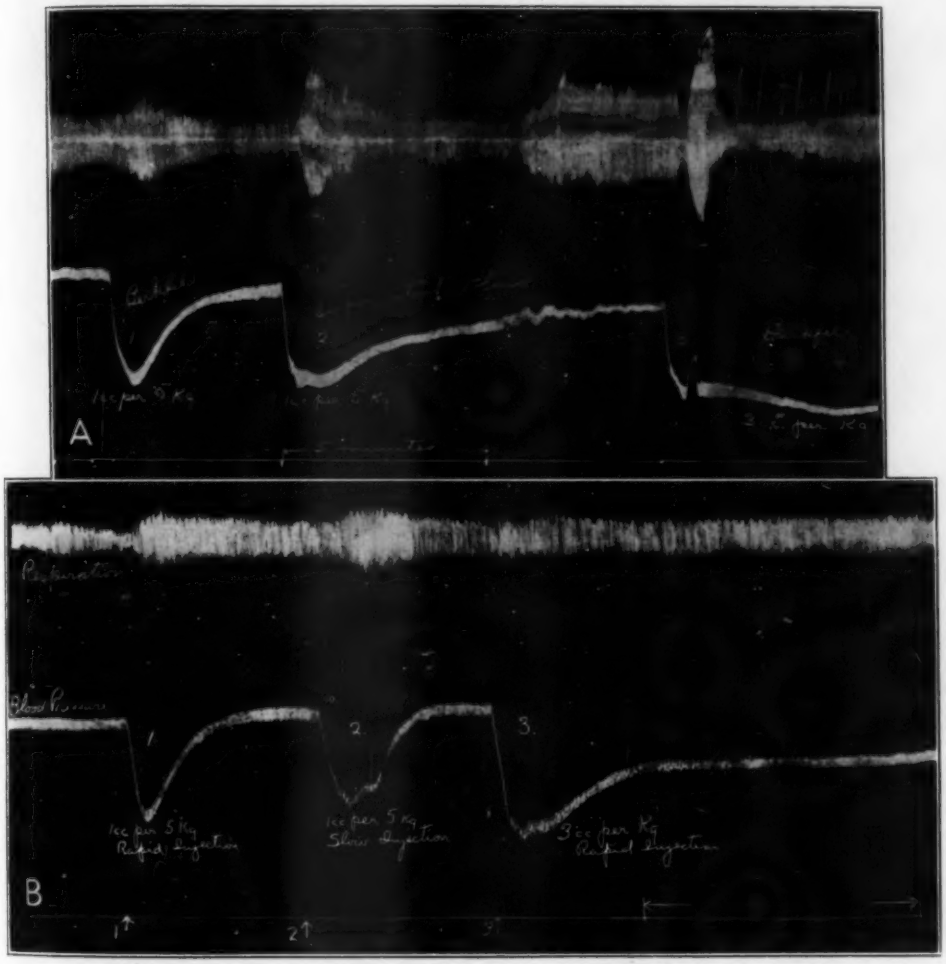

Fig. 4.—Kymograph series III, showing the toxicity of drainage material from an isolated duodenal loop. Intravenous injections were given to a dog under ether anesthesia. The spaces between the arrows represent five minute periods. *A* was obtained following the injection of bile-free drainage material from a loop so constructed as to contain pancreatic juice and duodenal secretion only; *B*, following the injection of drainage material from a duodenal loop receiving both bile and pancreatic juice.

appeared to be in good condition for three days during which time the drainage was collected into small rubber balloons for periods of several hours. This enabled

us to collect more than 200 cc. of secretion without overdistending the loop. At the end of four days the dog died. The loop was discolored but not perforated. There was no peritonitis or other grossly discernible cause of death. The toxicity of the stagnant contents was approximately the same as that of fresh specimens.

TABLE 3.—*Toxicity of Drained Pancreaticoduodenal Secretion*

Test Animal	Material Injected	Intravenous Dose*	Result
Dog 636	Drainage from duodenal loop, dog 624; supernatant fluid	3 cc.	Died in 12 hours
Dog 635	Drainage from duodenal loop, dog 624; Berkefeld filtrate	3 cc.	Died in 12 hours
Rabbit 45	Drainage from duodenal loop, dog 624; supernatant fluid	5 cc.	Died in 12 hours
Rabbit 43	Drainage from duodenal loop, dog 624; Berkefeld filtrate	5 cc.	Recovered

* Per kilogram of body weight.

TOXICITY OF OBSTRUCTED INTESTINAL CONTENT

Obstruction of any part of the small intestine produces at once a rapid accumulation of secretions which seems to be increased over the normal. Since reabsorption of fluid is never a major function of the small intestine, there ensues at once a metabolic disturbance due to loss of fluids, chlorides and other electrolytes, a phase of the problem which is now thoroughly appreciated and need not be discussed here. The present study concerns the effect of obstruction on the toxicity of the intestinal contents.

The material within the lumen of the obstructed intestine usually becomes brownish red or tarry, owing to decomposition of extravasated blood. It is foul-smelling and generally bad in gross appearance (the changes are due chiefly to bacterial putrefaction). The demonstrable toxicity of such material, however, is extremely variable. The variability is much greater than that noted in testing the normal contents. Concerning variations in toxicity observed under different conditions of obstruction, our experiments have demonstrated the following fact:

The contents of the obstructed bowel or of the isolated obstructed loop is less toxic than normal intestinal contents unless the obstructed segment receives and retains in concentrated form pancreatic duodenal secretion, in which case its toxicity may equal or exceed the normal.

Many previous investigators have recognized the fact that a high obstruction is more rapidly fatal than a low one.[7] We also find the contents of duodenal loops more toxic than that of other obstructions

7. Maury, J. W. D.: Death in Acute Intestinal Obstruction and Kindred Conditions is Due to Physiologic Disturbance: I. Has the Duodenum a Toxic Intestinal Secretion? J. A. M. A. **54**:5 (Jan. 1) 1910. Bunting, C. H., and Jones, A. P.: Intestinal Obstruction in the Rabbit, J. Exper. Med. **17**:192 (Feb.) 1913; ibid. **18**:25 (July) 1913.

and look on the pancreatic secretion as a probable explanation. The data which we outlined in the foregoing experiment and which we have verified repeatedly are further substantiated by experiments with isolated obstructed loops.

This method of study has long been employed in the investigation of intestinal obstruction. In this procedure, isolated obstructed loops of intestine are made by sectioning the bowel in two places, turning in the ends of the section thus isolated and restoring the continuity of the gastro-intestinal tract by anastomosis. The statement has been made that animals which have undergone such sectioning present the picture of an intestinal obstruction at the level of the isolated segment.[4] This is true only in part. In many instances an animal with an isolated loop of ileum will remain essentially normal for many weeks, dying only when the loop becomes gangrenous or perforated, causing generalized peritonitis. It is astonishing to note the size such a loop may attain and the quantity of foul material that may be contained within it. Yet the loop may remain normal except for the hypertrophy. In such a case the animal remains normal and recovers promptly if the loop is removed. These statements do not apply to duodenal loops. These loops rapidly become discolored and strangulated. Seldom, if ever, does an animal survive the sectioning of a duodenal loop more than sixty hours.

These sudden changes may be explained in part by the overdistention caused by the copious secretion which pours into such a loop chiefly from the pancreas. As indicated by previous experiments,[8] necrosis or gangrene of an intestinal loop may develop as a direct result of overdistention. However, the extremely rapid necrosis in these duodenal loops suggests the intensification of this process by another factor, namely, the autodigestion of the devitalized tissue by activated pancreatic juice. The gross and microscopic indications of acute hemorrhagic pancreatitis which we have observed furnish additional evidence that this process may be an important factor in the early death which occurs under these conditions. As shown in the protocol of dog 624, however, an animal with a pancreaticoduodenal loop dies even if the loop is drained, an observation pointing to the importance of metabolic disturbances as a factor in death from high obstruction.[9]

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8. Gatch, W. D.; Trusler, H. M., and Ayers, K. D.: Effects of Gaseous Distention on Obstructed Bowel; Incarceration of Intestine by Gas Traps, Arch. Surg. **14**:1215 (June) 1927.

9. Elman, R., and Hartman, A. F.: Experimental Obstruction of the Terminal Duodenum and Ileum: The Importance of Blood Chemical Changes in Causing Death, Surg., Gynec. & Obst. **53**:307 (Sept.) 1931. Wangensteen, O. H., and Chunn, S. S.: Studies in Intestinal Obstruction: III. Simple Obstruction: A Study of the Cause of Death in Mechanical Obstruction of the Upper Part of the Intestine, Arch. Surg. **16**:1242 (June) 1928.

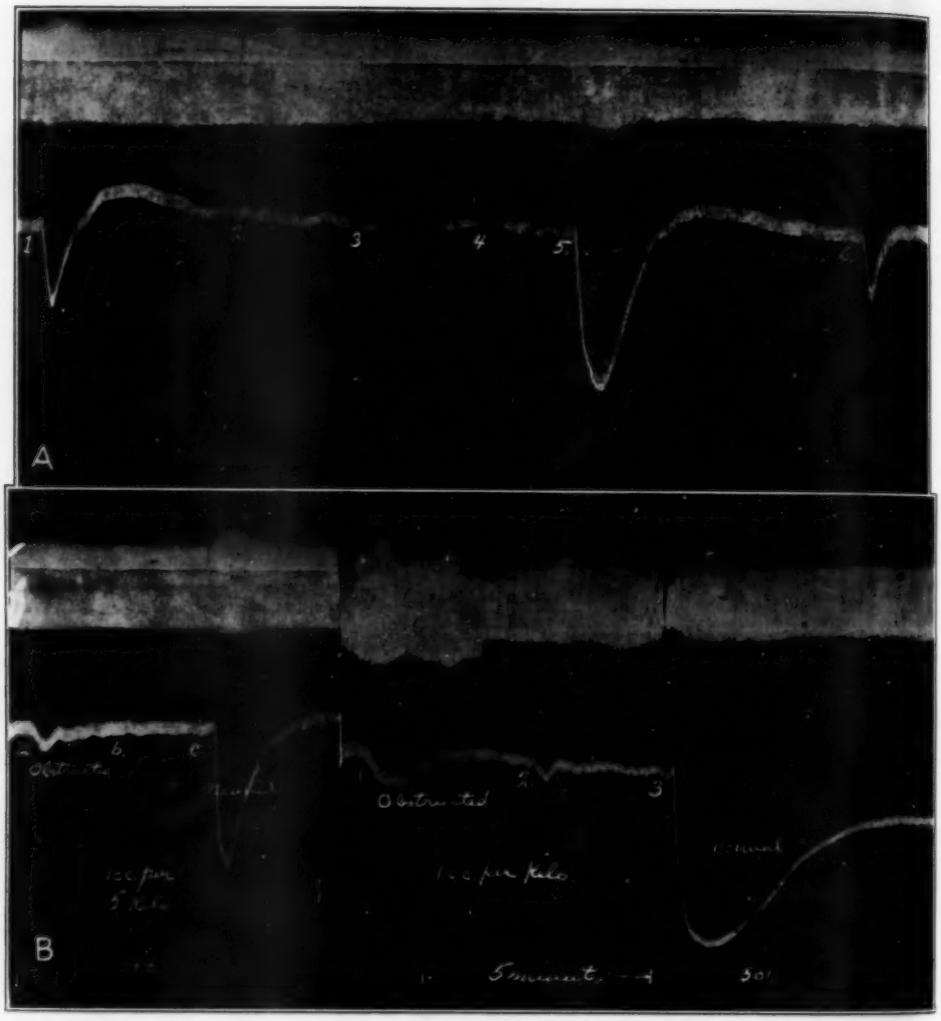

Fig. 5.—Kymograph series IV, showing the effects of the contents of obstructed intestine as compared with normal contents. Intravenous injections were given to a dog under ether anesthesia. *A* shows the results of the injection of a Berkefeld filtrate of the following material: *1.* Normal contents, dog 473, 1 cc. for each 5 Kg. *2.* contents of obstructed loop, dog 473, 1 cc. for each 5 Kg. *3.* Contents from above site of obstruction, dog 473, 1 cc. for each 5 Kg. *4.* Contents from above site of obstruction, dog 475, 1 cc. for each 5 Kg. *5.* Normal contents, dog 475, 1 cc. for each 5 Kg. *6.* Contents of obstructed loop, dog 475, 1 cc. for each 5 Kg. *B* shows slight toxicity of the contents of the obstructed intestine as compared with the normal contents in dog 475. A Berkefeld filtrate was employed.

As previously indicated, this study must be limited chiefly to a consideration of demonstrable toxicity in the contents removed. We studied, in all, sixty-eight isolated obstructed loops made at various levels of the bowel. In all the cases, with the exception of duodenal loops, we found Berkefeld filtrates of this material to be less toxic than similar preparations of normal intestinal contents. As compared to the normal contents, the filtrates of most samples from loops have no marked properties in lowering the blood pressure. Neither do they so commonly kill when injected intravenously into dogs and rabbits. Even the supernatant fluids which naturally contain large numbers of bacteria do not consistently kill on intravenous injection. Similar

TABLE 4.—*Toxicity of Contents of Obstructed Intestine as Compared with the Normal Intestinal Contents of Dogs*

Test Animal	Material Injected	Intravenous Dose*	Result
Dog 485	Sample 1; normal intestinal contents, dog 473; centrifugated supernatant fluid	3 cc.	Violent toxic symptoms; died in 20 hours
Dog 481	Berkefeld filtrate of sample 1.....	3 cc.	Toxic symptoms; recovered
Dog 486	Sample 2; contents from above site of obstruction, dog 473; supernatant fluid	3 cc.	Recovered
Dog 483	Berkefeld filtrate of sample 2.....	3 cc.	Recovered
Dog 487	Sample 3; contents of isolated obstructed loop, dog 473; supernatant fluid	3 cc.	Recovered
Dog 482	Berkefeld filtrate of sample 3.....	3 cc.	Recovered
Dog 497	Sample 4; normal intestinal content, dog 475; supernatant fluid	3 cc.	Died in 7 hours
Dog 496	Berkefeld filtrate of sample 4.....	3 cc.	Died in 48 hours
Dog 498	Sample 5; contents from above site of obstruction, dog 475; supernatant fluid	3 cc.	Recovered
Dog 499	Berkefeld filtrate of sample 5.....	3 cc.	Recovered
Dog 500	Sample 6; contents of isolated obstructed loop, dog 475; supernatant fluid	3 cc.	Died in 23 hours
Dog 495	Berkefeld filtrate of sample 6.....	3 cc.	Died in 48 hours

* Per kilogram of body weight.

samples of normal contents are much more consistently toxic than those from the obstructed loops. It is true that the crude material containing the tarry sludge so commonly formed in the obstructed loop is violently toxic on intravenous injection. Such material, however, is unsuitable for intravenous tests no matter what its source is.

Wangensteen [10] has previously reported the contents of an obstructed bowel to be less toxic than the normal, and our work, with the exceptions noted, bears out his observations. We consider it unnecessary to present our voluminous observations in detail. The limited data contained in tables 4 and 5, in addition to the kymographic records, present typical findings.

10. Wangensteen, O. H., and Chunn, S. S.: Studies in Intestinal Obstruction: I. A Comparison of the Toxicity of Normal and Obstructed Intestinal Content, Arch. Surg. **16**:606 (Feb.) 1928.

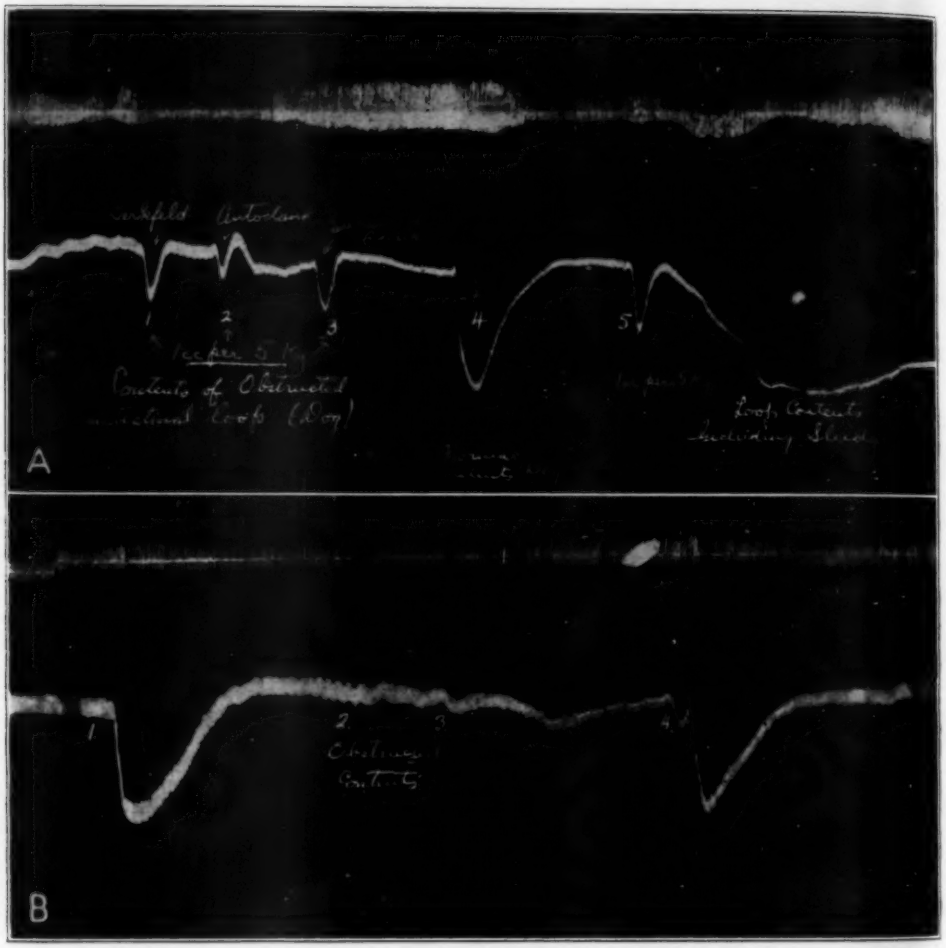

Fig. 6.—Kymograph series V. *A* shows the toxicity of the contents of obstructed intestine as compared with normal contents. The contents of dog intestine (1 cc. for each 5 Kg. of body weight) were injected intravenously into a dog under ether anesthesia. *B* shows the toxicity of the content of obstructed intestine as compared with drainage material from an enterostomy after operation. The following material (human intestine, case 1) was injected: *1.* Supernatant fluid, drainage material from enterostomy, 1 cc. for each 5 Kg. *2.* Supernatant fluid, contents of obstructed intestine, 1 cc. for each 5 Kg. *3.* Supernatant fluid, contents of obstructed intestine, 1 cc. per Kg. This injection produced no effect although the dose was increased five times. *4.* Supernatant fluid, drainage from enterostomy, 1 cc. for each 5 Kg.

In addition to the observations on dogs we have studied the contents of obstructed human intestine in sixteen cases. Most samples of this material possessed slight toxicity as compared to the drainage material which was subsequently obtained from the enterostomy above the obstruction. A few samples from obstructed bowel were found to be innocuous as portrayed in kymographic record V (fig. 6) showing the tests in case 1. In this patient after a few days the drainage material from the enterostomy acquired the toxicity typical of the normal con-

TABLE 5.—*Toxicity of Obstructed Intestinal Contents*

Test Animal	Material Injected	Intravenous Dose*	Result
Dog 569	Sample 1; supernatant fluid, contents of loop, dog 549†	3 cc.	Severe toxic symptoms; died in 4 hours
Dog 570	Berkefeld filtrate of sample 1.....	3 cc.	Mild symptoms; recovered
Dog 340	Sample 2; combined contents of several isolated obstructed loops of ileum; supernatant fluid	3 cc.	Mild symptoms; recovered
Dog 341	Berkefeld filtrate in sample 2.....	3 cc.	Mild symptoms; recovered
Rabbit 113	Supernatant fluid; sample 2.....	5 cc.	Died in convulsions
Rabbit 75	Berkefeld filtrate of sample 2.....	5 cc.	Recovered
Rabbit 38	Sample 3; contents of isolated obstructed loop of duodenum which was fatal to dog 603 in 48 hours; supernatant fluid	5 cc.	Immediate death
Rabbit 36	Berkefeld filtrate of sample 3.....	5 cc.	Toxic symptoms; recovered
	Tests on Content Above Site of Obstruction		
Dog 498	Sample 4; contents above site of obstruction in jejunum; supernatant fluid	3 cc.	Toxic symptoms; recovered
Dog 499	Berkefeld filtrate of sample 4.....	3 cc.	Mild symptoms; recovered
Rabbit 104	Sample 5; duodenal contents above site of obstruction at ligament of Treitz; supernatant fluid	5 cc.	Convulsions; died at once
Rabbit 117	Berkefeld filtrate of sample 5.....	5 cc.	Convulsions; died at once
Dog 292	Sample 6; contents above site of obstruction (ileum) in man, case 1; supernatant fluid	3 cc.	Died in 24 hours
Dog 294	Berkefeld filtrate of sample 6.....	3 cc.	Recovered
Rabbit 59	Supernatant fluid; sample 6.....	5 cc.	Died in 48 hours
Rabbit 61	Berkefeld filtrate of sample 6.....	5 cc.	Recovered

* Per kilogram of body weight.
† This was a 2 foot loop of high jejunum of dog 549 which survived for 9 days, at which time he was killed.

tents of the small bowel. In this case the enterostomy was high in the jejunum, and its drainage material would naturally contain a great amount of the combined pancreaticoduodenal secretions. Drainage from a low enterostomy usually shows less toxicity.

Proctocols—(Dogs 473 and 475).—Two dogs (473 and 475) were anesthetized with ether after twenty-four hours' starvation. In each animal the abdomen was opened; the jejunum was sectioned with the cautery about 8 inches (20 cm.) below the ligament of Treitz. The normal fluid contents of the duodenum and jejunum were collected and kept for testing. The jejunum was again sectioned about 3 feet (91 cm.) below Treitz's ligament. All the stumps were inverted, and no anastomosis was made. By this procedure we produced in each case a jejunal obstruction in addition to an isolated obstructed loop of jejunum.

Dog 473 was killed two days later, when in fair condition. The loop was intact but distended with a large amount of fluid. The contents of the loop and also the material above the site of the obstruction were tested and found much less toxic than the normal, as shown in table 4 and in kymographic record (fig. 5).

Dog 475 was explored at death, seven days after the obstruction. The loop was gangrenous and showed a small perforation, causing death from peritonitis. The contents of the loop were more toxic than in dog 473 (chemical studies showed the contents of the loop of dog 475 to contain large amounts of histamine). Neither the contents of the loop nor the material above the site of the obstruction was equal to the normal in toxicity.

GENERAL COMMENT

Many questions naturally arise from the foregoing observations. What are these toxic substances? Are they absorbed? If so, how and under what conditions? How can the reduced toxicity of the contents of the obstructed bowel as compared to that of the normal contents be explained? These are only a few, but even they cannot be answered in full at this time. By studies still in progress we hope to make further contributions, but at present we are justified in making only a few general comments.

Histamine produces effects comparable to the reaction we have described, and, as Gerard [11] reported, is present in varying but usually small amounts in practically all the samples of intestinal contents. We found, however, in our preliminary tests that samples of normal intestinal contents retain most of the toxic property after the histamine is removed. In filtrates of the contents of obstructed intestine which we tested similarly, the removal of histamine left little or no toxicity.

Concerning causes of the reduced toxicity in the obstructed intestine as compared to that in the normal bowel we haye no definite explanation. In the contents of low isolated obstructed loops it is obvious that little or no normal toxicity is present when the loop is formed, and the toxicity which is acquired must be due to bacterial putrefaction (the formation of histamine and other toxins). Under other conditions in which normal toxicity must be present in the contents at the outset, the disappearance or reduction in potency may be due to destructive putrefaction. There is the possibility, for which we have no proof, that the toxic substances may be removed by absorption.

As for this phase of the problem we have seen nothing to contradict the statements we have previously made that in simple obstruction, so long as the intestinal wall remains intact, there is no absorption of toxins sufficient to cause death.[2] When, however, the wall becomes gangrenous, there is ample evidence that any of these substances may slowly pass

11. Gerard, R. W.: The Lethal Agent in Acute Intestinal Obstruction, J. A. M. A. **79**:1581 (Nov. 4) 1922.

through transperitoneally, just as they are dialyzed through a dead membrane. As for the possibility that absorption may occur into blood or lymph with lesser degrees of injury from overdistention or strangulation, no satisfactory proof has been produced experimentally. However, the mere absence of such convincing evidence is not necessarily a proof of the negative. Even though toxins were absorbed, they might be destroyed or taken up by the tissues, or otherwise rendered undetectable. In fact, the transient effect on the blood pressure following intravenous injection is evidence that this must be to a large extent true.

Though these questions remain unanswered, the observations we have reported are somewhat enlightening. It appears that little significance need be attached to the finding of toxins in the obstructed bowel, when even more potent toxins are normally present within the lumen. Furthermore the statements to the effect that intravenous injection of these toxins leads to resecretion [12] into the upper part of the intestine are open to question on the same basis. We have investigated these claims and, as previously stated, we find the normal pancreaticoduodenal secretion more toxic than any material we have tested. Aside from this material we find no toxin secreted into the upper part of the intestine following the intravenous administration of contents of an obstructed bowel. In general, we find no basis for the assumption that intestinal obstruction leads to the formation of a specific toxin. We find toxic substances normally present within the lumen of the bowel, their chief source being the pancreaticoduodenal secretion. In high obstruction artificially produced in the dog we find definite evidence that necrosis and autolysis of tissue by activated pancreatic juice is the most important factor in the rapid death which occurs. We are not at present prepared to discuss this subject in full, and autopsy studies have not revealed pancreatic necrosis in fatal cases of intestinal obstruction in man.

It is quite apparent that many factors must be involved in the problem of intestinal obstruction, and nothing is gained by attempting to explain the mechanism of death on the basis of one single factor. Much valuable information has been accumulated in the past few years, and, on the whole, we have at least as many scientific data on the subject of acute intestinal obstruction as are available for any other problem in medicine. We are still attempting to solve the question, "Are toxins absorbed; if so, how and under what conditions?" But it seems likely that its solution is chiefly of academic interest. From a practical standpoint the chief cause of death in acute intestinal obstruction is the delay which so commonly preceeds the proper treatment.

12. Sweet, J. E.: Intestinal Obstruction, Experimental Research, Internat. Clin. **1**:72, 1920.

CONCLUSIONS

1. The normal contents of the bowel in dogs and in human subjects is always toxic when injected intravenously into animals.

2. Admitting the presence of many substances which may contribute to this toxic property, the chief source of the toxin appears to be the pancreaticoduodenal secretion.

3. The contents of the obstructed bowel or of an isolated obstructed loop is less toxic than the normal intestinal contents, unless the obstructed segment receives and retains in concentrated form the pancreaticoduodenal secretions, in which case its toxicity may equal or exceed that of the normal contents.

4. Methods of testing the material, the significance of the results obtained, the question of toxemia and other causes of death have been presented.

DIATHERMY AND REGENERATION OF BONE

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The value of heat as a potent agent in treating disease has long been recognized. Therapeutic heat is given in various ways; its penetration formerly depended on radiation from some hot, external object. With the advent of diathermy [1] a new form of application of heat was given to the medical profession. The value of diathermy theorectically depends on the development of heat within the tissues by the passage of a high frequency electric current through them. Whether there is some as yet unknown electromagnetic effect remains for further study, and does not fall within the scope of this paper. Because the heat is generated within the tissues, instead of coming from an external object, it should be more penetrating and, therefore, more effective than any other previous thermotherapy. Such claims are advanced in the literature, although since the time of d'Arsonval insufficient scientific investigation has been made to prove the actual penetrating qualities and mode of production of this heat and its effectiveness in the deeper tissues. In recent years much has been accomplished toward solving these problems, so that thermotherapy may now be more rational and be placed on a firmer scientific basis.

Much has been written concerning the value of diathermy in the treatment of fractures, especially in hastening delayed union. Of course, the disease causing the delay in union is an important consideration, but we believed that this problem should be studied first under as nearly normal conditions as possible. When we began these studies, we were skeptical as to the rise in deep temperature, particularly within osseous tissue—which is a poor conductor of electricity—and still more doubtful as to the value of diathermy in delayed union. A large amount of skepticism has been erased, as the microscope demonstrated an increase in formation of new bone when diathermy was used.

From the Surgical Hunterian Laboratory, Johns Hopkins University.

1. d'Arsonval, A.: Compt. rend. Soc. de biol. **43**:283, 1891.

Detailed reference to the literature will not be made. The experiments reported here were conducted for the purpose of determining: (1) whether there is an actual rise in temperature in bone when an extremity of an experimental animal is submitted to treatments with diathermy; (2) if there is a rise in the temperature of bone, whether this results in any demonstrable physiologic effect on bone in normal laboratory animals; (3) whether this physiologic effect, if present, hastens repair processes following injury to the bone.

The word "diathermy" is used as defined by the Council of Physical Therapy of the American Medical Association in the "Handbook of Physical Therapy." Diathermy is "the therapeutic use of a high frequency current to generate heat within some part of the body. The frequency is greater than the maximum frequency for neuromuscular response and ranges from several hundred thousand to millions of cycles per second."

EXPERIMENTAL WORK

The apparatus consisted of a spark gap generator, the maximum capacity of which was approximately 770 watts. The milliamperage employed in each experiment depended on the size of the forelegs of the animal used, and as a rule varied from 250 to 350 ma. In smaller animals the milliamperage required to raise the temperature of the skin to tolerance was about 200; in larger ones 400 or 500 ma. was occasionally demanded. The average time of application was thirty-five minutes a treatment.

The animals used in all experiments were healthy, normal dogs. The forelegs were chosen, in which the bones were more easily accessible and the experiments under better control. In the earlier experiments the bones of both legs were broken while the dog was under general anesthesia. On each side of the leg to be treated by diathermy a long, soft plate of lead foil was placed, under a plaster cast, after carefully shaving the skin. A similar cast, without the plates of lead foil, was placed on the opposite control leg. This was soon found impracticable, as the dogs constantly loosened the casts or chewed them off.

The most satisfactory and most easily controlled method of traumatizing the bone was that of boring a small hole, ⅛ inch (0.3 cm.) in diameter, through the large bone. This was done under general anesthesia with strict, surgical asepsis. The holes were drilled as nearly alike as possible and in corresponding positions in each leg. The wound in the control (right) leg was then sutured immediately. Into the hole in the left leg a small, clinical thermometer was inserted and another placed in the surrounding muscles. In a few instances a third thermometer beneath the skin, or between the diathermy electrode and the skin, indicated approximate subcutaneous or cutaneous temperatures. This was rather inaccurate and later abandoned. The edges of the skin and periosteum were brought together with interrupted black silk sutures, while the thermometers remained in place. Sterilized diathermy electrodes, consisting of rubber sponges surrounded by flexible brass mesh, were then applied on each side of the left leg, opposite the site of incision, and held in place by suitable, sterilized, wooden clamps (fig. 1). Sterile high frequency cords connected the electrodes to the generating apparatus.

After several trials to standardize technic it was found that the temperature in the bone could be raised to 101 or 102 F. without injuring the skin. The tem-

perature of the skin and muscles was always at first higher than that of the bone; later the temperature of the muscle fell a little, as a rule. In a few cases in which the temperature of the bone was raised to 105 or 106 F., secondary sloughing of the skin occurred. After arranging the apparatus, the current was turned on and gradually increased until the desired temperatures were obtained in about five minutes. The various settings of the machine were recorded on a chart for subsequent reference. Treatment was continued for an average of thirty minutes longer, making a total of thirty-five minutes for each treatment. These treatments were

Fig. 1.—Diathermy electrodes of brass mesh are put over rubber sponges and held in place by wooden clamps. For preliminary treatment (*A*) at operation all are sterilized by boiling, a precaution not necessary at subsequent treatments (*B*) when the wound is healed.

repeated each day for from one to four weeks, the same settings on the apparatus and the same amperage as was determined on the day of the operation being used. At the end of the various periods of treatment the dogs were killed for gross and microscopic studies of both the treated and the untreated bones.

OBSERVATIONS

Circulatory Changes.—During the immediate postoperative treatment with diathermy our attention was attracted by variations in bleeding from the open wound. This was carefully checked and found to be due

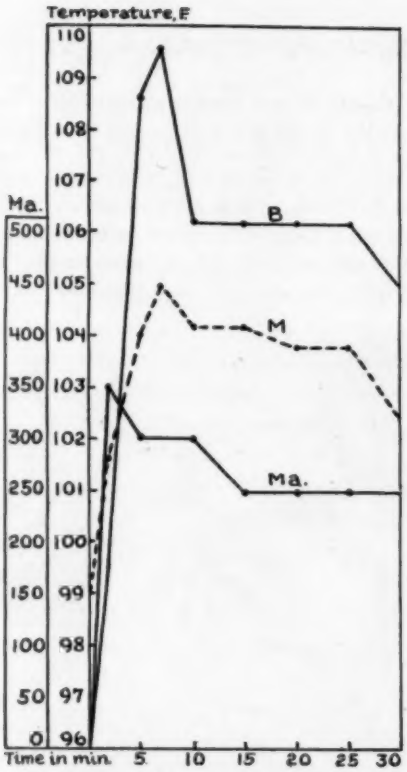

Fig. 2.—Graph showing changes in temperature in bone (*B*) and muscle (*M*), with variations in milliamperage (*Ma*).

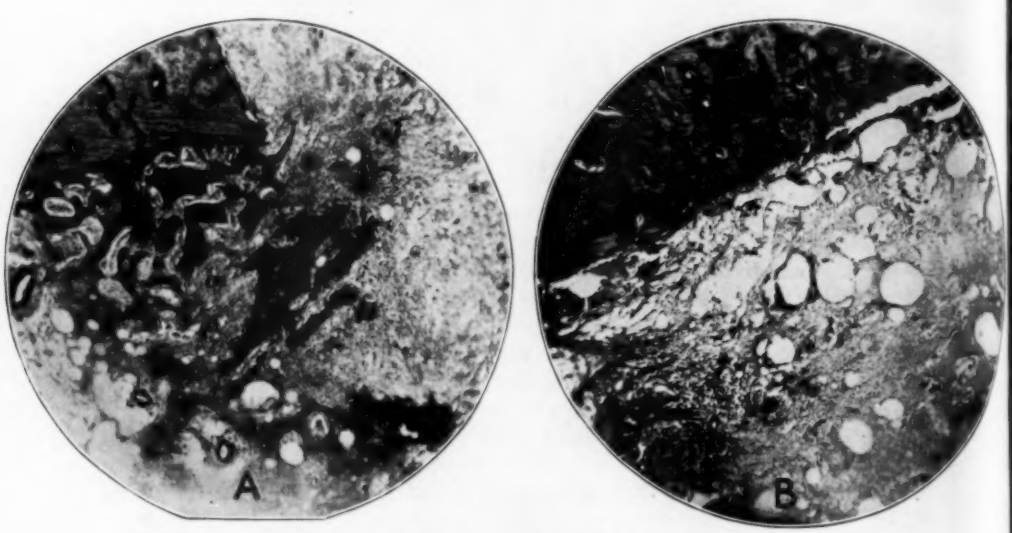

Fig. 3.—*A*, photomicrograph of the left leg after diathermy for one week, showing marked periosteal and endosteal formation of new bone. Note the highly vascularized marrow and numerous osteoblasts lining the newly formed trabeculae of bone. *B*, photomicrograph of the right leg after control observation for one week. Slight periosteal formation of new bone is seen.

to the treatment. Shortly after turning on of the current there was a free flow of blood, but as soon as the heat was discontinued and the leg allowed to cool a little, the bleeding stopped. This occurred with such regularity that we were forced to conclude that the heat or perhaps some other electromagnetic effect of the diathermy dilated the blood vessels, allowing free escape of blood into the wound. We assumed then that any beneficial effects, such as increased formation of new bone following diathermy, would probably be due to the increased circulation.

Diathermy electrodes, sterilized by boiling, were on one occasion applied while hot, water from the sterilizer being retained in the rubber sponges. As soon as these hot electrodes touched the leg a rapid rise in temperature occurred, in both the muscle and the bone, demonstrating that with such a small part of the body as the dog's forelegs, external heat will also raise the temperature of the bone. This seems to indicate that in these animals, at least, therapeutic effects can be obtained by the external application of hot objects. In clinical use, however, particularly in dealing with the large limbs of human beings, diathermy heat is more readily applied and probably penetrates more deeply. To prove this and to determine whether this type of external heat will stimulate formation of new bone, along with increasing temperature, require further investigation.

Considerable time was required and several animals were killed before our technic was sufficiently standardized for application to a well controlled series of animals. Nine dogs were used in the final group. Sloughing of the skin developed in one of these, so that it had to be eliminated. Our results, therefore, are based on eight successfully treated and controlled animals. During the first treatment, readings of the temperatures of the bones and muscles and the milliamperage were taken at the beginning of the experiment and every five minutes during the time that the current flowed. These readings were tabulated to form curves representing the rise and fall of the temperatures, with the rise and fall of the milliamperage as abscissas and the time as ordinates.

Figure 8 is a composite chart of the dogs in our series. The mean variations in milliamperage and the rises in temperature in the bones and muscles are all represented. It will be noted that, on the whole, the rise in temperature of the muscles and that of the bones are nearly parallel. The temperature of the muscles rises a little faster at first, to be overtaken later by the temperature of the bones, which, near the end of the experiment, again falls. These variations are hard to explain and for our purposes were not further studied. The main object of the investigation was to secure an actual rise in temperature in the bone, which we could reproduce at will by repeating the exact application of current determined at the time of the operation, which gave

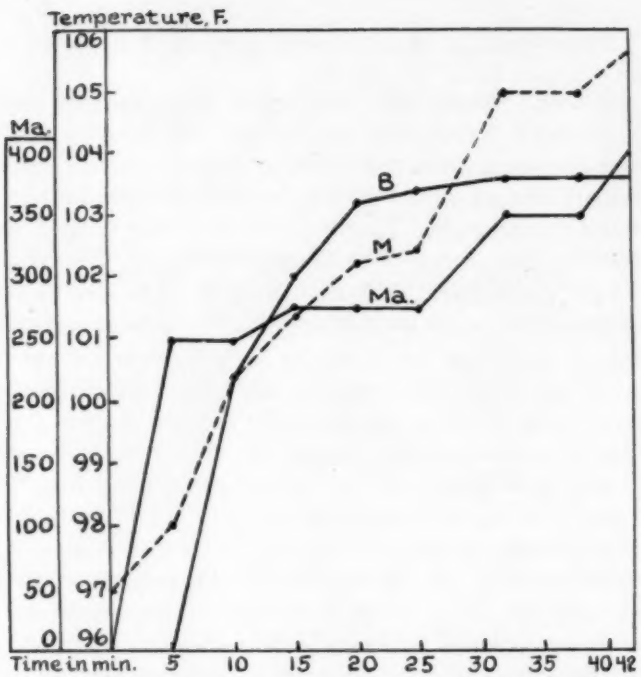

Fig. 4.—Graph showing changes in temperature in bone and muscle, with variations in milliamperage.

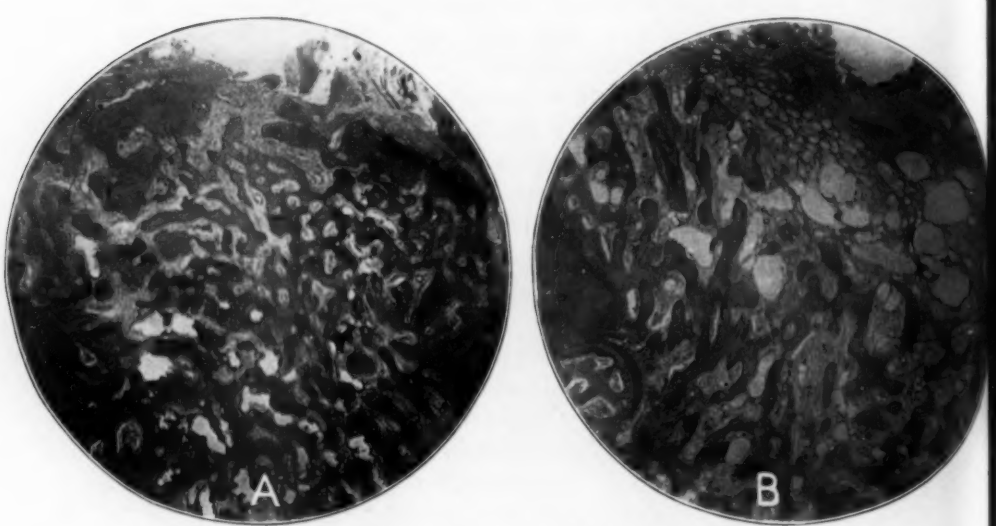

Fig. 5.—*A*, photomicrograph of the left leg after diathermy for two weeks. Note the rich periosteal and endosteal callus with a highly vascularized marrow which completely fills the region. *B*, photomicrograph of the right leg after control observations for two weeks. This section, from the region in which an osteotomy was done, is partially filled with endosteal callus. Note the almost complete absence of perisoteal callus.

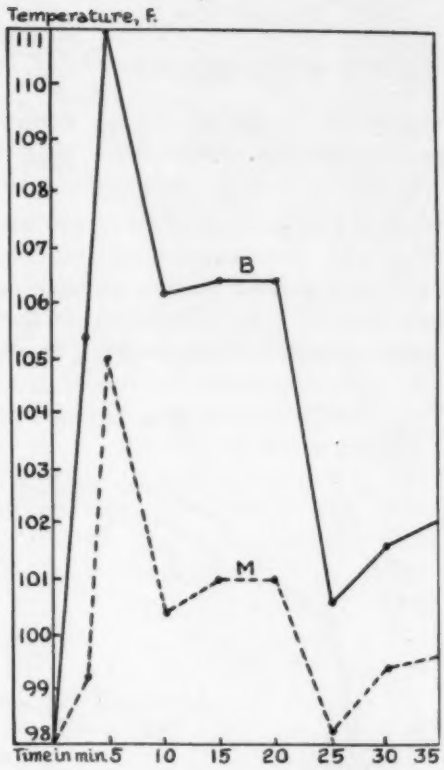

Fig. 6.—Graph showing changes of temperature in bone and muscle (skin).

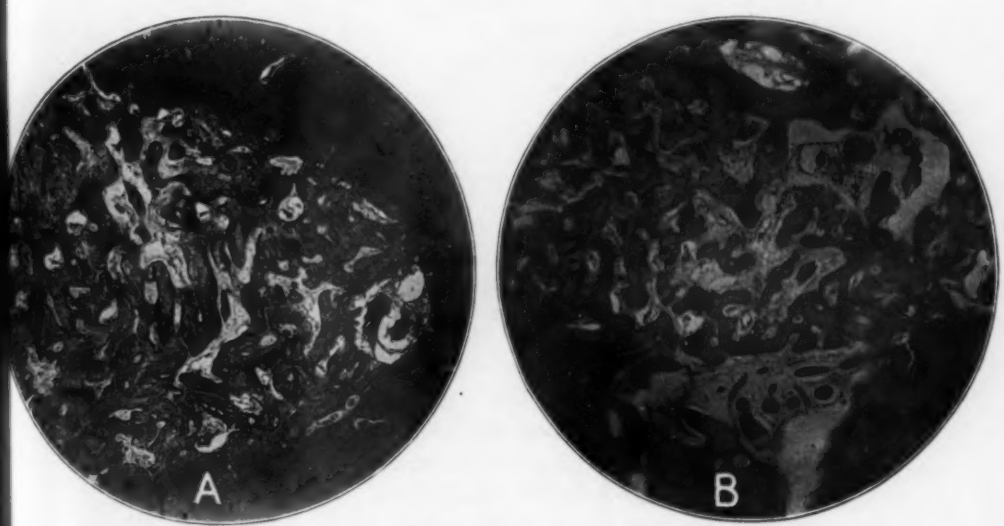

Fig. 7.—Photomicrograph of the left leg after diathermy for four weeks. The defect is almost completely filled by compact bone, rich in haversian canals. *B*, photomicrograph of the right leg after control observations for four weeks. The region in which osteotomy was done is filled with a newly formed lamellar type of bone arising mainly from the endosteum.

the rise in temperature in the bone above the normal and yet within physiologic limits. That this was obtained and gave definite beneficial results is verified by the results of the postmortem examinations.

Microscopic Changes.—One Week (figs. 2 and 3): In the treated leg the hole was filled with vascularized connective tissue, a few degenerated red blood cells and a small amount of bone dust. An attempt at formation of new bone was evident, arising from the cut edges of the endosteum. The endosteum in the neighborhood of the hole showed a

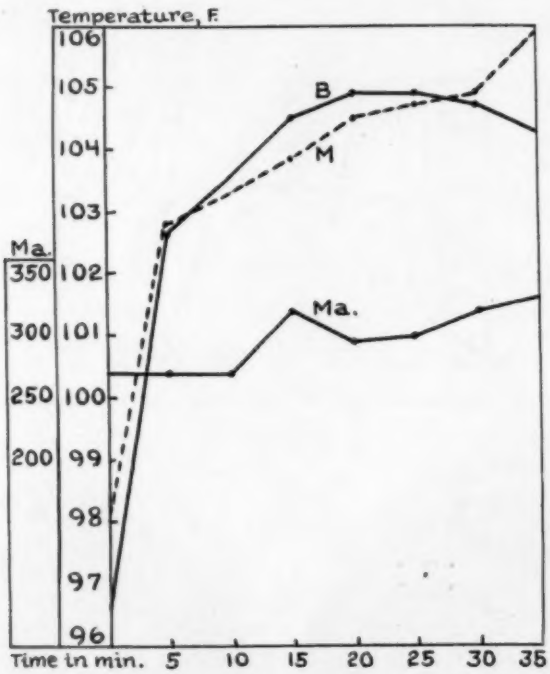

Fig. 8.—A composite chart of seven experiments showing average changes in the temperature of the bones and muscles, with variations in milliamperage and time, as determined at the operation. At subsequent treatments the same milliamperage was maintained, with the expected rise in temperatures of the bones and muscles.

marked proliferation of osteoid tissue extending down into the marrow cavity and the marrow cavity near the hole was filled with young fibrous connective tissue, which was highly vascularized.

In the control leg the hole was filled with a partially organized blood clot, fibrous connective tissue, degenerated red blood cells and bone dust, undergoing partial absorption. The cut edges of the endosteum were lined by fragmented bone with the bone cells missing. The cut edges of the cortical bone were lined by bone dust and fibrous connective tissue and occasionally by osteoblasts.

Two Weeks (figs. 4 and 5): The treated leg showed marked formation of new bone arising from the periosteum, the endosteum and the cut edges of the compacta. There was also evidence of formation of new bone in the marrow, with consequent narrowing of the medullary cavity.

In the control leg there was some periosteal new bone in the immediate neighborhood of the hole, with some osteoid tissue—not yet bone—arising from the cut edges of the endosteum. The cut edges of the compacta were lined with unabsorbed bone dust, with an occasional osteoblast. The medullary cavity was filled with blood and with bone dust partially absorbed by fibrous connective tissue.

Three Weeks: In the treated leg there was a decided advance in the periosteal and endosteal formation of new bone. The cut edges of the endosteum were lined with osteoblasts. There was a marked proliferation of bone in the medullary cavity, so that it was almost completely filled.

There is no periosteal new-bone formation, and only a slight amount of endosteal new bone in the control leg. The medullary cavity was far from being completely filled with bone. Along the site of the hole made by the drill the cavity was filled with a partially organized blood clot and some bone dust. Other portions of the marrow appeared to be normal, so that the osteogenesis was local.

Four Weeks (figs. 6 and 7): The treated leg revealed marked new periosteal bone. The hole was completely filled with a compact type of bone (not the young lamellar type) and looked like old cortical bone, except for an increase in haversian canals, which were more vascular and contained a larger number of young fibroblasts than usual.

In the control leg there was little or no periosteal new bone, and the hole was filled with a lamellar type of bone, so that it was not yet healed.

CONCLUSIONS

1. In experimental animals diathermy properly applied will raise the temperature of the bones and muscles.

2. The rise in temperature increases the local circulation.

3. Such increased physiologic activity accelerates the formation of new bone.

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LIPOMA PSEUDOMYXOMATODES OF THE UPPER EXTREMITY

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Atypical lipomatous tumors have been described under a variety of names, such as "myxoma lipomatodes," "lipoma myxomatodes," "myxofibrolipoma" and "myxosarcolipoma," according to the structure of the tumor and the pathologist's point of view. The literature shows that most of these atypical lipomatous growths occur in the intramuscular tissue of the lower part of the body, especially in the groin and upper thigh. The term "lipoma pseudomyxomatodes" has been applied to certain of these atypical tumors, the fat cells of which they are principally composed being immature and atypical, capable of proliferating and forming a syncytium-like structure and producing a mucoid intercellular substance.

The case reported here of a tumor of this type is of interest because of the unusual location of the growth and because, possibly, the histologic observations may be a contribution to the interpretation of the myxomatous changes taking place in the structure of the tumor mass.

REPORT OF A CASE

History.—J. E., a white man, aged 57, was admitted to Cook County Hospital on Oct. 11, 1932. The patient stated that he had always been well until six or seven years before admission, when a small soft swelling was observed on the posterior aspect of the left shoulder. It was painless and without other subjective symptoms. This swelling gradually increased in size until it was difficult for the patient to put on his clothes. No other swelling was observed at any time. The history disclosed no other important disease, but the right forearm had been amputated, following an injury.

Examination.—The patient did not appear to be acutely ill; there was no loss of weight; his appetite was good; no constipation or diarrhea was complained of. The head, neck and chest were normal, except for carious teeth. The abdomen was soft and relaxed and no masses were felt.

The cardiovascular and genito-urinary systems were normal. The urine had a specific gravity of 1.018, an acid reaction, a trace of albumin and occasional granular casts and pus cells, but no sugar. The blood pressure was 164 systolic and 98 diastolic.

From the Surgical Service of Cook County Hospital.

Fig. 1.—Lipoma pseudomyxomatodes; lateral aspect.

Fig. 2.—Lipoma pseudomyxomatodes; posterior view.

On the posterior aspect of the left shoulder was a soft mass larger than the patient's head. It was irregular in contour; expansible pulsation was not evident. The mass was crossed by many large, dilated veins and a large pulsating artery could be seen at the acromial border. The clinical aspects are portrayed in figures 1 and 2, which show the lateral and dorsal views of the tumor mass. Inspection and palpation of the tumor gave the impression that it was lipomatous.

Operation.—The tumor was found to be a large multilocular cystic mass, which was easily excised. The sutures were removed on the seventh postoperative day and the patient left the hospital in good condition on the following day. The postoperative course was afebrile.

The soft gelatinous mass removed measured 22 by 20 by 10 cm. and weighed about 1½ pounds (780.4 Gm.).

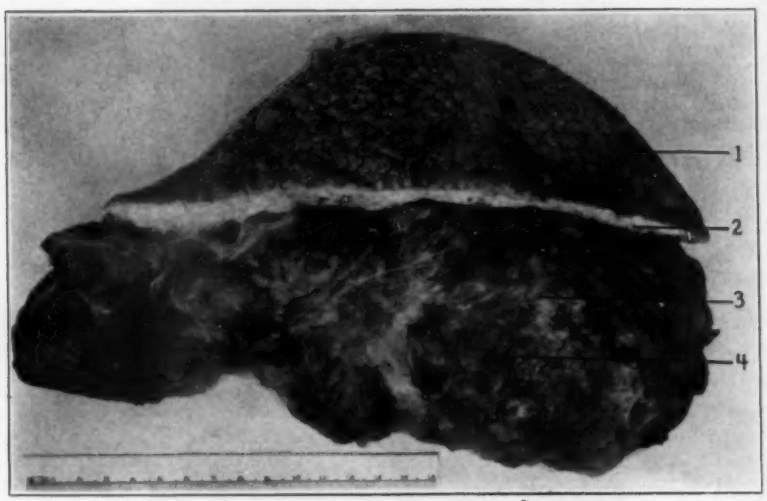

Fig. 3.—The excised tumor, showing (*1*) skin, (*2*) subcutaneous tissue, (*3*) lobules of intact fat tissue and (*4*) extensive areas of myxomatous degeneration.

Pathologic Examination.—The pathologist's report follows: "Macroscopic: The specimen is a large tumor mass 22 by 20 by 10 cm., which is covered on one side by a piece of skin and subcutaneous tissue measuring 12 by 20 cm. The tumor is moderately soft and fairly well circumscribed, although it has no definite capsule. The cut surface has a variegated appearance. Some areas are bright yellow, but most of the surface is light gray and mucoid in appearance, with stringy mucoid material exuding from it. There is a small amount of hemorrhagic mottling (fig. 3).

"Microscopic: Part of the section is composed of large fat cells with a delicate intercellular stroma. In many areas this stroma becomes loosened and slightly more cellular. The changes can be followed up to an extreme degree of interstitial loosening of the stroma, so that the tissue seems to be composed of an edematous fibrillar material in which the finest fibrils are individually isolated. A rich network of fibrils protrudes from each connective tissue cell. All of this tissue is embedded in a diffuse bluish-staining hyaline ground substance."

The diagnosis was lipoma pseudomyxomatodes.

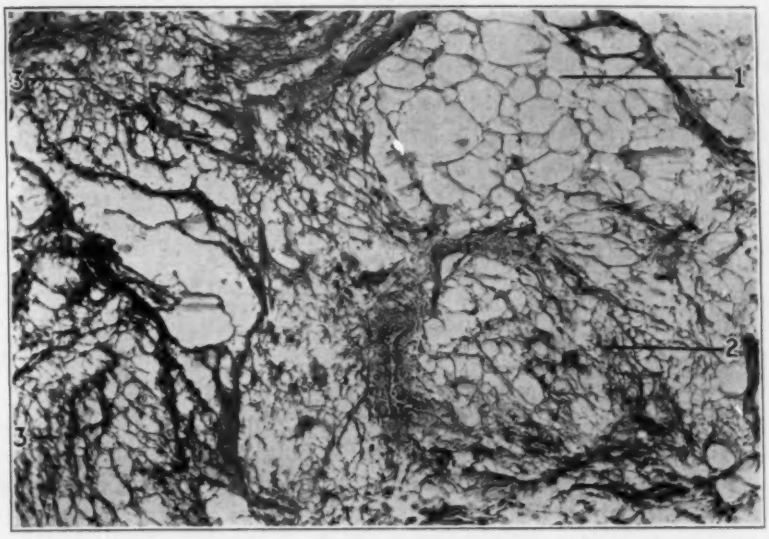

Fig. 4.—Photomicrograph of lipoma pseudomyxomatodes, showing (*1*) lipomatous tissue, (*2*) early myxomatous transformation and (*3*) advanced myxomatous metamorphosis; reduced from × 120.

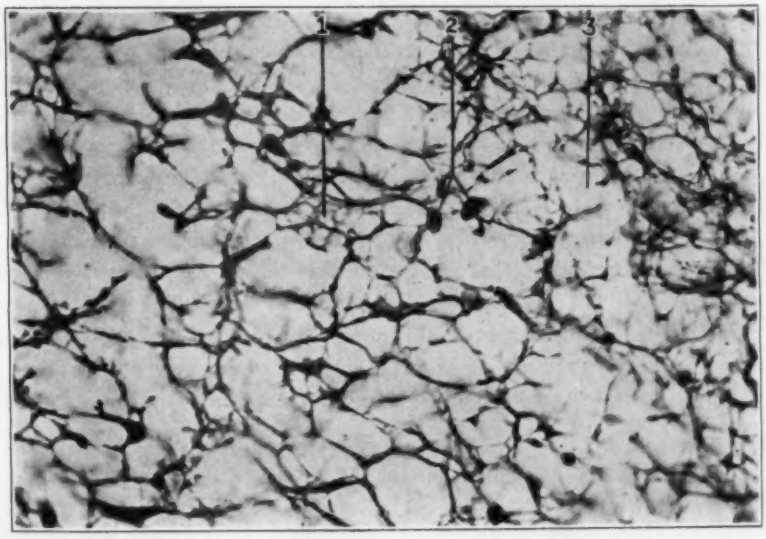

Fig. 5.—High power magnification (× 540) of myxomatous area, showing extensive fibrillar loosening of the myxoma-like cells, embedded in a mucoid ground substance: (*1*) extensive loosening and separation of the fibrils of the connective tissue; (*2*) nuclei of myxoma-like cells, and (*3*) mucoid ground substance.

COMMENT

Atypical lipomatous tumors, composed of mucinous and fat tissue, are not very rare. They may be benign or may have undergone malignant degeneration. In 1916 Robertson [1] collected reports of fifty-one cases from the literature. In seventeen of these cases the growth was situated retroperitoneally; in three it was in the mesentery and in most of the remainder it was in the leg or arm. Thirty-three per cent of the fifty-one tumors were malignant, and since 1916 many other malignant lipomatous tumors have been recorded.

Cases of atypical lipomatous tumor situated in the upper extremity are rather infrequent. Since Robertson's report I can find in the general literature record of only one case and this case was similar to ours. Rose,[2] a few years ago, reported a case of pedunculate lipoma situated on the inner side of the upper part of the arm of a woman (age not stated). The growth, which weighed 8½ pounds (3,855 Gm.), had been in existence for twenty-five years, and seemed to be undergoing mucoid degeneration. The pedicle contained several veins and one large artery.

The question of malignant changes in lipomatous tumors has received much attention. Pure lipomatous malignant tumors, such as the true liposarcoma, occur rarely and, according to many authors, it is probable that the lipomatous tissue is really a fatty degeneration of the sarcoma. For instance, in the case reported by Jaffé [3] the tumor was a sarcoma with extensive fat deposits in the cells. He therefore diagnosed the tumor as a liposarcoma.

On the other hand, the occurrence of true fatty degeneration has been denied. Lipvendahl [4] expressed the belief that it is out of the question: that lipomatous tumors chiefly occur in those parts of the body where the amount of fat is greatest; and he suggested that globules of fat are formed within the cells, coalescing and appearing as large bodies of fat in the cytoplasm. Moreover, there is the opinion defended by Jacobson [5] and others that under certain conditions mucin can be produced by fibroblasts; that in fact the fat cell is essentially a modified fibroblast.

Myxomatous degeneration of lipomatous tumors has been reported or suggested in a number of cases and has given rise to controversy as to what it really signifies. Jaffé [3] summarized the opinions expressed

1. Robertson, H. E.: Lipoma, J. M. Research **35**:131, 1916.

2. Rose, B. T.: A Case of Pedunculated Lipoma of the Upper Arm, Brit. J. Surg. **15**:525, 1928.

3. Jaffé, R. H.: Recurrent Lipomatous Tumors of the Groin, Arch. Path. & Lab. Med. **1**:381 (March) 1926.

4. Lipvendahl, R. A.: Liposarcoma of the Mammary Gland, Surg., Gynec. & Obst. **50**:81, 1930.

5. Jacobson, V. C.: J. Cancer Research **6**:109 (April) 1921.

in the literature in reporting a case of lipoma pseudomyxomatodes. He stated that, as shown by the histologic examination in his case, the mucoid parts of the tumor were not true myxoma tissue but areas of mucoid degeneration resulting from an extensive edematous loosening of the connective tissue. Hence the name "lipoma pseudomyxomatodes." However, that this is not merely an ordinary degenerative change is evident by the presence of many centers of growth, consisting of young, immature fat cells. It is these young and immature, rapidly growing fat cells that undergo myxomatous transformation. But these fat cells are different from the cells of a true myxoma. According to Jaffé the close relationship between myxomatous and fat tissue during embryonic life explains the observation that fast-growing immature fat cells sometimes resemble mucin cells without really being transformed into them. In the present case figure 5 shows very clearly the early and advanced myxomatous transformation of lipomatous tissue.

It appears that there are some questions still to be settled in regard to the nature of atypical lipomatous tumors, especially of the class known as lipoma pseudomyxomatodes.

CHROMAFFIN CELL TUMOR CAUSING PAROXYSMAL HYPERTENSION, RELIEVED BY OPERATION

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AND

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The first satisfactory description of a chromaffin cell tumor (otherwise known as paraganglioma, perithelioma or pheochromocytoma) is credited to Berdez [1] in 1892. These tumors occur usually in the suprarenal medulla, but have been found in other locations in which there may be chromaffin tissue. This tissue is distinguished, as its name implies, by its affinity for chromates, which stain the cells brown. It has its embryonic origin in sympathetic ganglion cells which in turn are the result of migration and differentiation of cells from the neural crest. It is embryologically and functionally distinct from suprarenal cortical tissue.

Epinephrine being secreted by chromaffin cells, it is not surprising that tumors of this tissue should be associated with hypertension. In 1897 Neusser [2] described two patients—one a man of 25 years—both of whom died of cerebral hemorrhage and in whom no cause for hypertension was found other than tumors of the suprarenal bodies (carcinomatous degeneration). He definitely postulated that in these cases hypertension was caused by an increased production of the physiologically active secretion of the suprarenal bodies.

However, these tumors are rare. The early reports consisted almost solely of histologic descriptions of the tumors. Even in more recent reports the clinical descriptions have often been incomplete, the tumor having been accidentally discovered at autopsy; the reported clinical findings have not been constant, and different anatomic diagnoses have been associated with similar clinical conditions.

It seems desirable to attempt to clarify the situation and to establish a basis for clinical diagnosis if possible. If the condition is diagnosed, these cases are amenable to surgical cure because the tumors, in almost all cases, have been well encapsulated and are free from metastases.

From the Departments of Medicine and Surgery, the University of Michigan.

1. Berdez: Contribution à l'étude des tumeurs des capsules surrénales, Arch. d. méd. expér. et d'anat. path. **4**:414, 1892.

2. Neusser, E.: Die Erkrankungen der Nebennieren, in Nothnagel, H.: Spezielle Pathologie und Therapie, Vienna, Alfred Hölder, 1897, vol. 18, p. 71.

A number of the more recent cases which have been reported in detail have had a striking clinical picture in which the hypertension has occurred in paroxysms with a characteristic symptomatology. There have also been symptoms suggestive of the paroxysmal hypertensive syndrome in some of the other cases about which information is not as complete.

It is our purpose in this paper to report a new case of chromaffin cell tumor with paroxysmal hypertension in which resection of the tumor gave relief, and to review the cases about which there is some clinical information. The present case is the fourth one in which there has been relief by surgical intervention. In two of those with relief by operation the condition was not diagnosed as chromaffin cell tumor, but the cases seem to belong in this group for reasons which will be discussed later.

REPORT OF CASE

C. S., a boy, 16 years of age, entered the University Hospital with the chief complaint of attacks of dyspnea, sweating, headache, precordial oppression, nausea and vomiting. These attacks had occurred two or three times a week over a period of five months prior to his admission. They occurred usually at night and came on without apparent cause. An attack lasted several hours. Between attacks the patient felt well except for some dyspnea and palpitation on exertion. The history was irrelevant except for asthma in May and June every year since the age of 6 months. There had been nocturia (once or twice a night) for one and one-half years.

Physical examination revealed a fairly well developed and well nourished boy. The pupils were regular and equal and reacted normally in accommodation. Ophthalmoscopic examination showed endarteritis and periarteritis with fresh and old hemorrhages. There was a considerable degree of oral sepsis. The apical impulse of the heart was palpable 10 cm. to the left of the midsternal line in the fifth intercostal space. The heart sounds were regular and of good quality. There was a loud, blowing systolic murmur, with maximum intensity in the second intercostal space just to the left of the sternum, also heard over the entire precordium. The blood pressure was 125 systolic and 105 diastolic. Examination of the lungs gave entirely negative results. Palpation of the abdomen revealed no masses, palpable organs or areas of tenderness. There was no edema of the extremities. The reflexes were normal.

The Kahn reaction of the blood was negative. Repeated specimens of urine showed an intermittent albuminuria, some specimens showing as much as 3 plus albumin. Casts in varying quantities up to 10 per low power field were found from time to time. Hemoglobin determinations and the red cell, white cell and differential counts were normal. Elimination of phenolsulphonphthalein was 52 per cent in two hours. A concentration test disclosed an ability to concentrate to a specific gravity of 1.023. An electrocardiogram showed a sinus tachycardia and inversion of the T waves in leads I and II. Roentgenograms of the chest demonstrated peritruncal infiltration extending into both apexes. An orthodiagram showed the size of the heart to be within the limits of normal variation. Ordinary roentgenograms of the kidneys and pyelograms showed no definite abnormality.

Following the patient's admission it was noticed that coincident with the attacks there was a marked fluctuation of blood pressure. This is well illustrated by figure 1, in which the blood pressures determined every few minutes over a two-hour period are recorded. Figure 2 shows the routine daily blood pressure determinations. Later in the course of the patient's illness the rapid fluctuations were no longer observed, the blood pressure rising to a level between 280 and 340 systolic and remaining at this level, with minor fluctuations, for several hours before dropping again to within normal limits. During the attacks the patient perspired profusely. The extremities were cold and clammy. The lips appeared slightly cyanotic. The patient complained of headache, precordial oppression or pain, dyspnea and occasionally epigastric pain associated with nausea and vomiting. Examination of the heart and lungs during the attack revealed no changes

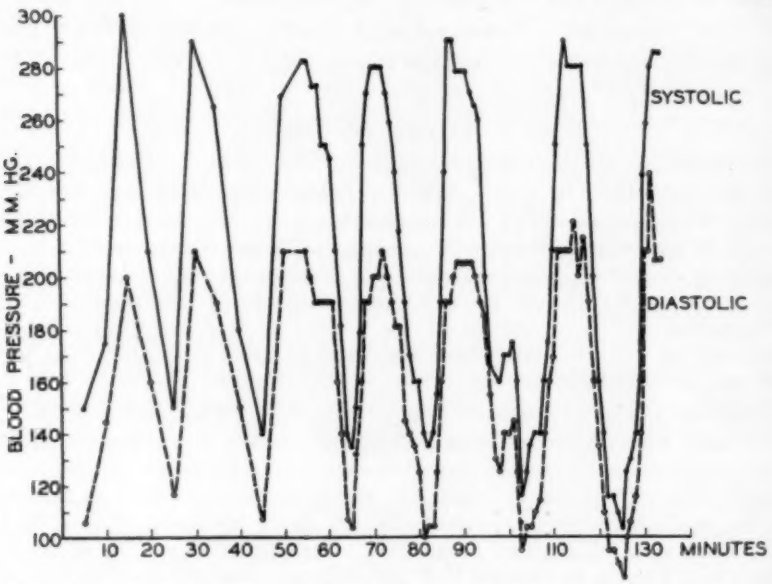

Fig. 1.—Marked fluctuations of the blood pressure during a paroxysm of hypertension.

other than the slowing of the heart rate, which was a constant accompaniment of the hypertensive phases. There was no elevation of blood sugar or nonprotein nitrogen during the attacks. The effect of various drugs on the paroxysms of hypertension was noted, and the only striking effect was that produced by the inhalation of amyl nitrite, which caused a sudden drop in pressure of from 100 to 150 mm. with an associated severe sensation of dizziness. The effect of epinephrine given in the intervals between the attacks was also noted; the patient showed marked hyposensitiveness to epinephrine as compared with the effects noted by Jensen [3] in normal and hypertensive persons given injections of the drug.

As time went on the patient's attacks became more severe and more frequent, occurring almost daily. During one attack acute pulmonary edema developed, with

3. Jensen, J.: Adrenalin Test in Hypertension, Am. Heart J. **5**:763 (Aug.) 1930.

the expectoration of considerable quantities of frothy, blood-stained sputum. It was decided at this time that exploratory laparotomy, performed in the hope of discovering a suprarenal tumor, should not longer be delayed.

The anesthetic chosen was nitrogen monoxide and oxygen. However, on administration of this anesthetic, the patient suddenly collapsed, becoming markedly cyanotic and pulseless. Recovery followed the administration of oxygen.

Two days later the patient was again prepared for operation, and on this occasion was given ether anesthesia. The condition remained satisfactory during the induction, although after the operation began, the blood pressure rose from 150 systolic and 120 diastolic to 300 systolic and 140 diastolic in an hour's time. A midline incision 3 inches (7.6 cm.) long was made just above the umbilicus. The peritoneum was opened. Exploration revealed the left kidney to be essentially normal in outline, although the upper pole seemed somewhat firmer than usual.

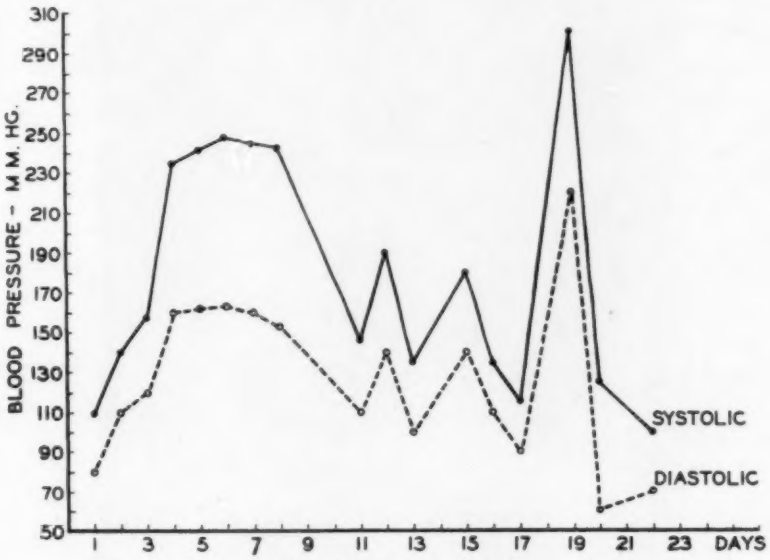

Fig. 2.—Routine daily determinations of the blood pressure.

The spleen, liver, gallbladder, stomach and duodenum were normal to palpation. On the anterior aspect of the right kidney was a firm tumor about 8 cm. in diameter, lying lateral and superior to the hepatic flexure. A transverse incision was then made from the medial incision through the entire abdominal wall back to the peritoneal gutter on the right side. The tumor, as shown in figure 3, was directly under the peritoneum and occupied the anterior aspect of the kidney, lying on it without being attached to it. Its blood supply came entirely from the surrounding peritoneum and retroperitoneal tissues and not from the kidney. The renal capsule was intact. The suspensory folds of the hepatic flexure were incised and the colon retracted downward and mesially. The peritoneum was lifted and the tumor removed with ease. The peritoneum was reconstructed and the abdominal wall sutured in layers.

Shortly following the removal of the tumor the blood pressure dropped rapidly until no pressure readings could be obtained. The patient was given dextrose solution, 5 per cent, intravenously, and a saline infusion. This resulted in a tem-

porary circulatory revival, with a blood pressure reading of 95 systolic and 60 diastolic. But within a short time again no blood pressure readings were obtainable. Following transfusion the patient's condition improved markedly, the blood pressure rising to 115 systolic and 85 diastolic. The condition of the patient then remained good, and further measures to combat shock were not found necessary.

The report of the pathologist (Dr. C. V. Weller) on the tumor was as follows: This neoplasm is made up of polyhedral cells with spherical nuclei and foam structure which are arranged in small alveolar nests in relationship to the blood

Fig. 3.—Drawing of the operative field showing the relative size and position of the tumor.

vessels. This resembles some of the tumors associated with precocious puberty. It is unlikely to have given rise to metastases at its present stage of development. Chromate fixation shows a striking affinity for the chromate salts, indicating relationship to the chromaffinic system rather than to suprarenal cortical structures.

In the six months since the operation the patient has been entirely free from attacks such as he previously suffered. He has been able to resume all the activities of a boy of his age without unusual dyspnea. During two periods of observation in the hospital frequent blood pressure determinations have almost all ranged between 120 systolic and 80 diastolic and 130 systolic and 90 diastolic. Evidence of recovery from the vascular effects of hypertension in the ocular fundi and

kidneys is of interest. Ophthalmoscopic examination shows improvement in the retinal vessels. There is no evidence of fresh hemorrhages or active inflammatory changes. The urine has been consistently free from albumin, very few red blood cells have been found, and the kidneys now show an ability to concentrate to a specific gravity of 1.036.

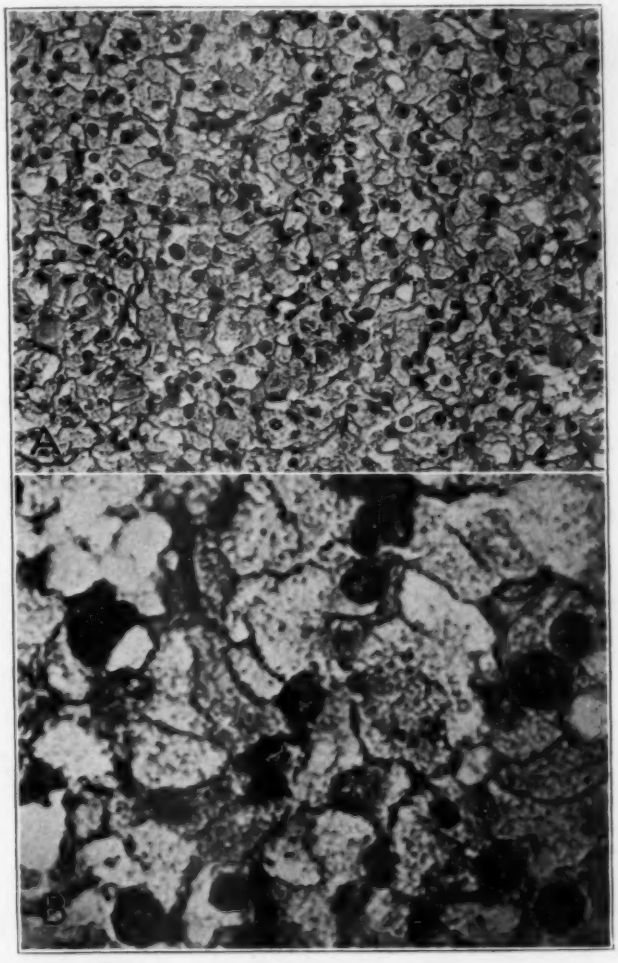

Fig. 4.—*A*, photomicrograph of a section of the tumor, low power magnification; *B*, photomicrograph of a section of the tumor, high power magnification, showing the large polyhedral cells, with cytoplasm of foam structure and chromaffin granules.

CASES FROM THE LITERATURE

We have been able to collect seventeen cases with the diagnosis of chromaffin cell tumor in which there were blood pressure determinations or in which the size of the heart was known. Another case (12) with-

out this information is listed because the symptom, rather frequent attacks of suffocation, is suggestive of paroxysms of hypertension. Two cases (19 and 20) in which other diagnoses were made are also listed because the well described paroxysmal hypertension which they showed was so similar to that of known cases of chromaffin cell tumor, proved by the chromate stain, that they seem to belong in this group. (We shall discuss later the difficulty in histologic diagnosis if chromate fixation with its characteristic brown staining of the chromaffin cells is not practiced.) These cases have been classified according to the action of the chromate stain on the tumor tissue.

A. *Positive Chromate Stain.*—Case 1 (Herde [4]).—No clinical data were given for this patient, a woman, 62 years of age. The heart weighed 225 Gm.

Case 2 (Herde [4]).—The patient was a man, 45 years of age. No clinical data were given. The heart, which was "much enlarged," weighed 460 Gm.

Case 3 (Helly [5]).—A man, 43 years of age, had a condition of the heart which for a long time was regarded as "nervous," but finally was called "kidney heart." The blood pressure was described as being considerably elevated. There was intermittent glycosuria. The heart was extraordinarily hypertrophied, especially the left ventricle.

Case 4 (Hausmann and Getzowa [6]).—A man, 53 years of age, had dyspnea and frequently coughed up bloody sputum. The blood pressure was not known. There was slight glycosuria which disappeared. Death was caused by influenzal pneumonia. The heart weighed 445 Gm., and there was hypertrophy, predominantly of the left ventricle.

Case 5 (Biebl and Wichels [7]).—A man, 36 years old, had repeated attacks of semiconsciousness. He showed: polyuria and thirst; glycosuria, 5.5 per cent, and acetone, +. The blood pressure ranged from 208 systolic and 128 diastolic to 225 systolic and 125 diastolic. Paroxysms of hypertension were not observed. The heart weighed 450 Gm.

Case 6 (Oberling and Jung [8]).—A woman, 28 years of age, was pregnant (at term) and complained of violent headache. There were no vasomotor or cardiac symptoms except slight edema of the legs. There were rapid fluctuations of the blood pressure, without apparent cause, from 170 systolic and 125 diastolic to 220 systolic and 155 diastolic, a condition described as paroxysmal hypertension.

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4. Herde, M.: Zur Lehre der Paragangliome der Nebenniere, Arch. f. klin. Chir. **97**:937 (April 4) 1912.

5. Helly, K.: Zur Pathologie der Nebenniere, München. med. Wchnschr. **60**: 1811 (Aug. 19) 1913.

6. Hausmann, M., and Getzowa, S.: Ein Paragangliom des Zuckerkandl'schen Organs mit gleichzeitiger Herz- und Nierenhypertrophie, Schweiz. med. Wchnschr. **3**:889 (Sept. 7) and 911 (Sept. 14) 1922.

7. Biebl, M., and Wichels, P.: Physiologische und pathologisch-anatomische Betrachtungen im Anschluss an einen Fall von Paragangliom beider Nebennieren, Virchows Arch. f. path. Anat. **257**:182 (July 31) 1925.

8. Oberling, C., and Jung, G.: Paragangliome de la surrénale avec hypertension paroxystique, Bull. et mém. Soc. méd. d. hôp. de Paris **51**:366 (March 24) 1927.

The blood pressure was once 250 systolic and 190 diastolic. Death occurred from shock following delivery. The heart weighed 450 Gm.

CASE 7 (Rabin [9])—A woman, 45 years of age, for ten years had had palpitation and dyspnea on slight exertion and tremor of the hands. The range of blood pressure in several determinations was 177 systolic and 122 diastolic to 226 systolic and 108 diastolic. The heart weighed 515 Gm., and all the chambers were hypertrophied and dilated.

CASE 8 (Schröder [10]).—A woman, 42 years old, for five years had suffered from sweats and attacks of faintness. For one and a half years she had had diabetes, which was considered to be refractory to insulin. There was no acetonuria. The blood pressure was 220 systolic and 140 diastolic. No paroxysms were observed. Autopsy revealed left ventricular hypertrophy.

CASE 9 (Pincoffs and Shipley [11]).—A woman, 26 years of age, had attacks of constriction over the heart, palpitation, dyspnea, nausea, vomiting, headache and tremor associated with paroxysms of hypertension in which the systolic rate advanced to 260 mm. of mercury. Between attacks the blood pressure was normal (120 systolic and 90 diastolic). Surgical removal of the tumor brought relief of the symptoms.

CASE 10 (Barker [12]).—A man, 46 years of age, showed weakness and mental disturbance and had had recurring convulsions for three months. The blood pressure was 200 systolic and 114 diastolic. Paroxysms of hypertension were not observed. Physical examination revealed the heart to be enlarged.

B. *Negative Chromate Stain.*—CASE 11 (Orth [13]).—The symptoms were not reported. The blood pressure was from 180 systolic and 115 diastolic to 230 systolic and 140 diastolic. Paroxysms were not observed. The heart showed marked hypertrophy and dilatation, especially of the left ventricle. The presence of epinephrine in extract of the tumor was shown by a test on a frog's eye.

CASE 12 (Masson and Martin [14]).—A woman, 45 years of age, suffered from emaciation, pain in the right side of the abdomen and frequent attacks of suffoca-

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9. Rabin, C. B.: Chromaffin Cell Tumor of the Suprarenal Medulla (Pheochromocytoma), Arch. Path. **7**:228 (Feb.) 1929.

10. Schröder, K.: Eine doppelseitige chromaffine Nebennierengeschwulst mit Hypertonie, Virchows Arch. f. path. Anat. **268**:291 (June 20) 1928.

11. Pincoffs, M. C.: A Case of Paroxysmal Hypertension with Suprarenal Tumor, Tr. A. Am. Physicians **44**:295, 1929. Shipley, A. M.: Paroxysmal Hypertension Associated with Tumor of the Suprarenal, Ann. Surg. **90**:742 (Oct.) 1929.

12. Barker, L. F.: Cystic Tumor of the Medulla of the Suprarenal Gland (Paraganglioma), Associated with Early and Persistent Arterial Hypertension, with Arterial Thickening, and with Multiple Hemorrhages within the Central Nervous System, Causing Epileptiform Convulsions, Paralyses, and a Psychopathic State, M. Clin. North America **14**:265 (July) 1930.

13. Orth, J.: Ueber eine Geschwulst des Nebennierenmarks nebst Bemerkungen über die Nomenklatur der Geschwülste, Sitzungsb. d. Preuss. Akad. d. Wissensch. **1**:34, 1914.

14. Masson, P., and Martin, J.: Paragangliome surrénal. Etude d'un cas humain de tumeurs malignes de la médullo-surrénale, Bull. Assoc. franç. p. l'étude du cancer **12**:135, 1923.

tion. The blood pressure is not known, but the attacks suggest paroxysms of hypertension. The tumor was a surgical specimen. No autopsy was allowed.

CASE 13 (Zeckwer [15]).—A woman, 56 years of age, had right hemiparesis, with acute softening. The blood pressure is not known. The heart was not said to be enlarged on physical examination or at autopsy.

CASE 14 (Handschin [16]).—A man, 45 years of age, had a blood pressure of 140 systolic. Clinical symptoms of hypertension were not described. Death was caused by bronchopneumonia, following extirpation of a carcinoma of the stomach. The heart was not included in the examination at autopsy.

CASE 15 (Wichels and Biebl [17]).—A man, 33 years of age, for five years had had headaches and attacks of unconsciousness with biting of the tongue. The blood pressure was 225 systolic and 130 diastolic. Paroxysms were not noted. Death occurred from bronchopneumonia. The heart weighed 450 Gm., and the left ventricle was hypertrophied.

C. *Chromate Stain Not Done.*—CASE 16 (Labbé, Tinel and Doumer [18]).—A woman, 28 years of age, for several months had had attacks of epigastric constriction, vomiting, pallor and sweating, with paroxysms of hypertension in which the blood pressure rose to 280 systolic and 190 diastolic. She had two attacks of pulmonary edema. The blood pressure was extremely irregular; it was usually moderately elevated, although once it fell as low as 120 systolic and 80 diastolic. Death occurred with pulmonary edema. The heart weighed 340 Gm.

CASE 17.—(Labbé, Azérad and Violle [19]).—A man, 29 years of age, had paroxysms of hypertension with tachycardia, violent palpitation, pallor and sweating. The blood pressure was ordinarily around 160 systolic and 100 diastolic, but it rose to 300 or more during the paroxysms and remained there for an average of one hour. The heart weighed 350 Gm., and examination showed dilatation and hypertrophy of the left ventricle.

CASE 18 (Bergstrand [20]).—A woman, 50 years of age, died of influenzal pneumonia. The previous symptoms and blood pressure were not known. The heart weighed 500 Gm.

D. *Cases with Paroxysmal Hypertension; Tumor not Diagnosed as Chromaffin Cell Tumor; Chromate Stain Not Done.*—CASE 19 (C. H. Mayo [21]).—A woman, 30 years of age, had attacks of dyspnea, palpitation, tachycardia, tightness in the

15. Zeckwer, I. T.: Chromaffin Cell Tumor of the Adrenal Medulla (Paraganglioma), Boston M. & S. J. **193**:254 (Aug. 6) 1925.

16. Handschin, E.: Zur Kenntnis der Zuckerkandl'schen Organe, Beitr. z. path. Anat. u. z. allg. Path. **79**:728 (April 16) 1928.

17. Wichels, P., and Biebl, M.: Zur Diagnose der Paragangliome der Nebennieren, München. med. Wchnschr. **75**:656 (April 13) 1928.

18. Labbé, M.; Tinel, J., and Doumer: Crises solaires et hypertension paroxystique en rapport avec une tumeur surrénale, Bull. et mém. Soc. méd. d. hôp. de Paris **46**:982 (June 29) 1922.

19. Labbé, M.; Azérad, E., and Violle, P. L.: Adénome médullaire surrénal et hypertension paroxystique, Bull. et mém. Soc. méd. d. hôp. de Paris **53**:952 (July 8) 1929.

20. Bergstrand, H.: Suprarenal Tumor with Hypertrophy of the Heart, Hygiea **82**:321 (May 31) 1920.

21. Mayo, C. H.: Paroxysmal Hypertension with Tumor of Retroperitoneal Nerve, J. A. M. A. **89**:1047 (Sept. 24) 1927.

chest, headache and vomiting, with a rise of blood pressure from 130 systolic and 82 diastolic to 300+ systolic and 180 diastolic, pallor, sweating, frothy, bloody sputum and signs of pulmonary edema. A tumor was removed surgically, which brought relief from the attacks. Pathologic examination revealed the tumor to be a malignant blastoma.

CASE 20 (Porter and Porter [22]).—A man, 39 years of age, had attacks in which he felt "terrible"; he experienced an unpleasant sensation in the epigastrium, and his color was ashen. The systolic blood pressure would rise from 110 to 200 or more, with a slow (about 55), forcible heart beat. Surgical removal of the tumor brought relief of the symptoms. Pathologic examination revealed a suprarenal adenocarcinoma and suprarenal hypernephroma.

COMMENT

Of the ten cases yielding a positive chromate stain, nine showed evidence of hypertension. In six cases (5, 6, 7, 8, 9 and 10) there were recorded systolic blood pressures of 200 mm. of mercury or over. In another (case 3) a "considerable elevation" of the blood pressure was described, and at autopsy there was "extraordinarily marked hypertrophy" of the heart, especially of the left ventricle. In two other cases (2 and 4) with unrecorded blood pressure, the weights of the hearts were 460 and 445 Gm., respectively. In one (case 1) the symptomatology and blood pressure are not known, but the heart weighed only 225 Gm.

Of three cases in which the chromate fixation was not done, the two reported by Labbé and his co-workers (16 and 17) showed characteristic paroxysms of hypertension. The hearts were moderately hypertrophied, weighing 340 and 350 Gm., respectively. In the third case (18) the blood pressure was not known, but the heart weighed 500 Gm.

There were five cases in which a diagnosis of chromaffin cell tumor was made despite a negative chromate stain. In some the failure of the stain was explained by delay in obtaining and fixing the specimen (in our case the chromate stain was well marked in tissue which had stood unfixed, at room temperature, for twenty-four hours). In two of these five cases (11 and 15) hypertensions of 230 systolic and 140 diastolic and 225 systolic and 130 diastolic, respectively, were recorded. In the third (case 12) there is no information regarding blood pressure or the size of the heart, but the attacks of suffocation from which the patient suffered are suggestive of paroxysmal hypertension. In two cases (13 and 14) there is no evidence of hypertension or cardiac hypertrophy in the reported findings.

Therefore, in all except three of twenty cases, there was either known hypertension or indirect evidence of it. In two of the three cases

22. Porter, M. F., and Porter, M. F., Jr.: Report of a Case of Paroxysmal Hypertension Cured by the Removal of an Adrenal Tumor, Surg., Gynec. & Obst. **50**:160 (Jan.) 1930.

without evidence of hypertension, the chromate stain was negative. We suggest that this may have been because of insufficient differentiation of the cells, and that for the same reason the cells may not have attained their function of secretion of epinephrine.

Hypertension alone would not serve to identify these cases clinically. But in six of the cases previously reported (6, 9, 16, 17, 19 and 20) and in our case it occurred in paroxysms with a fairly constant set of symptoms suggestive of a sudden large dosage of epinephrine. During the attack the patient complained of coldness of the extremities, precordial oppression, palpitation, dyspnea, headache, tremors and frequently nausea and vomiting. There were marked pallor and sweating. The blood pressure rose to an extremely high level, with the systolic rate frequently over 300 mm. of mercury. Both tachycardia and a slow forceful heart beat were noted. Frothy, blood-stained sputum with signs of pulmonary edema occurred a number of times. The attacks in two cases were thought to be initiated by exercise or by assuming certain positions. In the others they occurred without apparent inciting cause. The duration of an attack was from one to several hours. Between attacks the patient was usually asymptomatic, and the blood pressure was commonly normal, although in two cases it was usually observed to remain moderately elevated. This may have been due to insufficiently frequent and improperly timed determinations. Albuminuria and glycosuria occurred irregularly in some cases.

In the other cases the reported clinical data are inadequate to identify such paroxysms. In six of them some symptom was noted which is more or less suggestive of the occurrence of paroxysms. In case 4 there was frequent bloody sputum suggestive of the attacks of pulmonary edema which have been noted. The patient in case 5 had repeated attacks of semiconsciousness; the sweats and attacks of faintness in case 8 and the attacks of suffocation in case 12 are reminiscent of the symptoms described in recognized paroxysms. The patient in case 10 had recurring convulsions for three months, while in case 15 the patient had headaches and attacks of unconsciousness with biting of the tongue. The elevation of blood pressure may be so extreme in these cases that hypertensive encephalopathy would not be surprising.

It is possible that the paroxysmal nature of the hypertension was overlooked in cases in which it could have been demonstrated by more complete observations. Unless the recognition of the symptoms leads to such observations or unless frequent blood pressure determinations are made at the right times it can be readily overlooked. This is well demonstrated by figure 2 which shows daily routine determinations of blood pressure over a period of twenty-two days made in our case. A somewhat similar curve of blood pressures, showing usually a moderate

to severe hypertension is charted for case 16. It will remain for future observations to determine how common the paroyxsmal hypertensive syndrome is in cases of chromaffin cell tumor. Its recognition seems to offer the only possibility of diagnosis and cure of this condition.

In addition to the two cases in which the diagnosis was not chromaffin cell tumor, but which were included in the list because of the characteristic paroxysmal hypertensive syndrome, there have been other reports of suprarenal cortical cell tumors which were associated with hypertension. Oppenheimer and Fishberg [23] collected nine such cases and added two of their own: a clinical case (with sexual precocity) and one coming to autopsy. A priori, these are difficult to understand. No pressor substance is known to be elaborated by the suprarenal cortex. One might speculate on the possibility of mechanical stimulation of the medulla by such tumors, causing an abnormal secretion of epinephrine. This, however, has not been observed in the not infrequent metastatic carcinoma of the suprarenal glands. Herde [4] in 1912 warned against the danger of a wrong diagnosis. Speaking of the chromaffin cell tumors, he said: "All these tumors have in common a rather uniform alveolar structure. The alveoli are generally separated by narrow connective tissue septums, often only by capillaries, so that pictures result which have great similarity to Gravitz' hypernephroma." Dr. C. V. Weller, in the routine pathologic examination of the specimen from our case, noted its resemblance to cortical tumor. It could readily have been diagnosed as such save for the chromate staining. In none of the cases collected by Oppenheimer and Fishberg was the use of the chromate stain reported. It would seem impossible to accept as proved such cases in which the chromate stain is not used.

The cases of cortical tumor with sexual precocity as well as hypertension are more difficult to dispose of. There were three such cases in the series collected and reported by Oppenheimer and Fishberg. However, Dr. C. V. Weller [24] said that sexual precocity has been seen not only in primary cortical cell tumor but also in metastatic neoplasms of other types invading the suprarenal glands. It would seem that judgment on these cases also must be withheld pending further observations with the chromate stain.

Paroxysmal hypertension has been reported in a few cases in which other conditions than chromaffin cell tumors have been present. Weber [25] reported a case of subacute meningococcic meningitis in which

23. Oppenheimer, B. S., and Fishberg, A. M.: The Association of Hypertension with Suprarenal Tumors, Arch. Int. Med. **34**:631 (Nov.) 1924.

24. Weller, C. V.: Personal communication to the authors.

25. Weber, C.: L'hypertension artérielle paroxystique au cours d'une méningite méningococcique subaiguë, autopsie, Arch. d. mal. du cœur **20**:598 (Sept.) 1927.

there were marked paroxysms of hypertension. Harvier and Bariéty [26] observed a case in which paroxysms of hypertension were associated with a carcinoma of the esophagus and were attributed to vagus irritation. Another similar case is that of Villaret and his co-workers [27] with a lymphosarcoma of the mediastinum. C. Aubertin [28] reported several cases of angina pectoris and of rheumatic heart disease associated with mild paroxysms of hypertension. However, these cases showed obvious pathologic processes and usually did not have associated with the paroxysms of hypertension symptoms simulating the clinical syndrome noted in the cases of chromaffin cell tumor. They should seldom be cause for confusion.

SUMMARY AND CONCLUSIONS

A new case of paroxysmal hypertension with chromaffin cell tumor which was relieved by operation has been presented and the literature reviewed.

Hypertension has been a feature in most of the reported cases of chromaffin cell tumor. In five of those previously reported, as in our case, it occurred in paroxysms with a clinically recognizable symptomatology. In others, some symptoms suggestive of such paroxysms have been noted. Subsequent observations may show the paroxysmal hypertensive syndrome to be a more constant characteristic than previous reports demonstrate.

Hypertension has also been noted in cases with a diagnosis of tumor of the suprarenal cortex. Chromaffin cell tumors may simulate cortical tumors so closely in histologic appearance that diagnoses which are not confirmed by chromate staining must be questioned until substantiated by subsequent cases in which chromate fixation is practiced.

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26. Harvier, P., and Bariéty, M.: Forme laryngée du cancer de l'œsophage. Crises hypersensitives d'origine laryngée, Bull. et mém. Soc. méd. d. hôp. de Paris **49**:176 (Feb. 6) 1925.

27. Villaret, M.; Bloch, S.; Bariéty, M., and Lappas: Crises hypertensives paroxystiques au cours d'un lymphosarcome du mediastin supérieur, Bull. et mém. Soc. méd. d. hôp. de Paris **50**:1215 (July 9) 1926.

28. Aubertin, C.: Hypertension paroxystique et œdème aigu du poumon, Bull. et mém. Soc. méd. d. hôp. de Paris **52**:1768 (Dec. 20) 1928; L'hypertension paroxystique dans l'angine de poitrine, J. méd. franç. **16**:49 (Feb.) 1927.

TUBERCULOSIS OF THE APPENDIX

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In the four and one-half year period between July 1, 1928, and Dec. 31, 1932, 3,271 appendectomies were performed at the Koster Clinic; 4 appendixes showed tuberculosis. Tuberculosis of the appendix is one of the more rare manifestations of infection with the Koch bacillus in the human body. Corbin,[1] in 1837, was the first to observe such a case. In 1838, Hallowel [2] reported a death from peritonitis due to perforation of a tuberculous appendix. Following these observations a number of reports on tuberculosis of the appendix, cecum or both appeared at intervals. Koch's discovery of the tubercle bacillus, in 1882, greatly increased the impetus to the study of tuberculosis generally, and subsequently observations on this subject were reported more frequently. However, it was not until 1909, when Muller [3] published his excellent monograph on tuberculosis of the appendix, that any definitely collective statistical study was made. He collected 66 instances. In 1 case the patient died as a direct result of the operation, while in others patients died within a few months following the operation. In fact, in only 8 cases were the patients reported cured. In 1917, Scott [4] was able to find but 44 articles on the subject, 9 of which had been contributed by physicians of the United States. Since 1917, 39 articles have been written on tuberculosis of the appendix or on tuberculosis of both the appendix and the cecum or adnexa.

The late John B. Deaver considered tuberculosis of the appendix a very rare disease, while Lockwood of England and the late John B. Murphy believed that 2 per cent of all diseased appendixes are tuberculous. They also believed that if enlarged mesenteric glands are found the infection with the Koch bacillus is primary in the appendix. The frequency of tuberculosis of the appendix found at operation is given in table 1.

The frequency of tuberculosis of the appendix found at necropsy, according to Muller,[3] is given in table 2.

From the Koster Clinic, Crown Heights Hospital.

1. Corbin, M.: Gaz. méd., Paris **5**:639, 1837.
2. Hallowel, E.: Am. J. M. Sc. **22**:127, 1838.
3. Muller, G. P.: Univ. Pennsylvania Bull. **22**:48, 1909-1910.
4. Scott, J. R.: Ann. Surg. **66**:648, 1917.

According to Noehren and Mueller,[5] of 515 appendixes which came under observation in the State Institute for the Study of Malignant Disease in Buffalo, 23, or 4.4 per cent, were tuberculous.

Muller [3] stated that the disease is more common in males than in females, the ratio being 3:2. In our series of 4 cases 2 of the patients were males, and 2 were females. Most of the cases reported in the literature occurred in young adults. The lymphoid tissue in the appendix of the young adult is more abundant and the mucous membrane more delicate. Heller,[6] in a series of autopsies, found intestinal tuberculosis in 12 per cent of the adults and 26 per cent of the children. Hueppe [6]

TABLE 1.—*Frequency of Tuberculosis of the Appendix Found at Operation*

Surgeons or Institution	Year	Number of Operations	Number of Tuberculous Appendixes	Percentage
Fitz	1886	257	8	3.0
Robson	1902	300	5	1.7
Letulle	1905	300	2	0.7
Mayo	1905	1,888	29	1.5
Surgical Laboratory, University of Pennsylvania	1909	310	6	2.0
Deaver	1902-1913	7,610	16	0.2
Allen	1909	89	2	2.8
Montreal General Hospital	1909	12,003	71	0.5
Mayo	1914	1,259	3	0.1
Scott	1917	179	1	0.5
University of Minnesota Hospital	1916-1919	210	2	0.9
Free Hospital for Women, Brookline, Mass.	1902-1932	7,865	9	0.1
Koster Clinic	1928-1932	3,271	4	0.1

TABLE 2.—*Frequency of Tuberculosis of the Appendix Found at Necropsy*

Pathologist or Institution	Number of Autopsies	Number of Tuberculous Appendixes	Percentage
Fenwick and Dodwell	2,000	17	0.8*
Leseur	500	144	22.0
Kelly	3,770	44	1.2
White	56	33	59.0

* Primary tuberculosis of the appendix.

stated that the number of cases of primary intestinal tuberculosis may be reckoned as between 25 and 35 per cent of all cases of tuberculosis in children which end in death. While Fenwick and Dodwell [7] found the ileocecal region involved in 85 per cent of their autopsies on 2,000 patients with phthisis, in only 9.6 per cent was it the sole seat of the disease.

Eisendrath,[8] in 1908, reported 51 instances of tuberculosis of the appendix which he had collected from the literature and added 7 of his

5. Noehren, A. H., and Mueller, T.: Surg., Gynec. & Obst. **34**:215, 1922.
6. Quoted by Ravenel, M. P.: Proc. Path. Soc. Philadelphia **10**:73, 1907.
7. Fenwick, W. S., and Dodwell, P. R.: Lancet **2**:133, 1892.
8. Eisendrath, D. N.: The Acute Forms of Abdominal Tuberculosis, J. A. M. A. **52**:291 (Jan. 23) 1909.

own. In 1909, Muller [3] reviewed the literature and found 60 cases reported; he added 6 others that came under his observation. Scott,[4] in 1917, reported 68 cases recorded in the literature and added 1 of his own, bringing the total number of cases to 69, but he did not mention Porter's [9] case, reported in 1913, and Wilkins' [10] 2 authentic cases, reported in 1917, which we include in our review. Since then there have been no collected statistics on tuberculosis of the appendix. We have reviewed the literature and have collected all the authentic instances of tuberculosis of the appendix from 1917 to the present. We have not included any case clinically diagnosed as tuberculosis of the appendix in which an appendectomy was not performed and the appendix examined histologically. Cases of miliary tuberculosis with generalized involvement of all the organs, including the appendix, are not included.

REPORT OF CASES

The cases reported were as follows:

Porter (1913).[9]—A woman, aged 28, complained of pain in the right lower quadrant of the abdomen. Examination revealed pulmonary tuberculosis and a tender mass in the right lower quadrant of the abdomen. Laparotomy showed a mass made up of the ileum, cecum and adherent omentum. Resection of the terminal part of the ileum, of the cecum and a part of the ascending colon and ileocolic anastomosis were performed. The pathologic report was: ulcerative ileocecal tuberculosis, with involvement of the appendix. The patient was discharged from the hospital, but died five months later of bronchopneumonia.

Wilkins (1917)[10].—Case 1.—A man, aged 26, complained of recurrent attacks of abdominal pain. Examination revealed tenderness and a small fixed mass in the right lower quadrant. At laparotomy a small curled-up appendix covered with omentum and adherent to the lateral wall of the pelvis was found. When the adhesions were separated a small amount of pus was found. There was no involvement of the cecum or lymphatic glands. Pathologic examination revealed tuberculosis of the appendix. The patient made a good recovery and was well to the time of the report. There was no pulmonary tuberculosis.

Case 2.—A woman, aged 31, complained of frequent shooting pains in the right lower quadrant of the abdomen. Examination revealed tenderness near McBurney's point, with a small fixed mass near the right anterosuperior spine. Laparotomy revealed a small curled-up appendix adherent to the parietal peritoneum, covered with omental adhesions which, when separated, revealed a few drops of pus. The cecum and lymphatic glands appeared normal. The pathologic report was: tuberculosis of the appendix. There were no signs in the lungs. The patient was well following the operation to the time of the author's writing.

Case 3.—The author described a third case but the specimen was lost.

Emmert (1918)[11].—A farmer complained of attacks of pain in the right lower quadrant of the abdomen, resembling appendicitis. He had pain in the right side on the least jarring. A roentgenogram of the chest revealed pulmonary tubercu-

9. Porter, M. F.: J. Indiana State M. A. **6**:113, 1913.
10. Wilkins, G. C.: Tr. New Hampshire M. Soc. **126**:80, 1917.
11. Emmert, M.: Nebraska M. J. **3**:62, 1918.

losis. The appendix was removed, and the patient recovered and was well thereafter. A pathologic report showed that the appendix was tuberculous.

Gatewood (1920)[12].—A man, aged 39, complained of recurrent attacks of pain in the right lower quadrant of the abdomen. Examination of the chest gave negative findings. A mass was suspected in the right lower quadrant; there were tenderness and rigidity on deep palpation. Laparotomy revealed that the omentum and ileum were bound down to the appendix and cecum. The cecum felt infiltrated. Appendectomy was performed. The pathologic diagnosis was: hyperplastic tuberculosis of the appendix.

Warwick (1920)[13].—Case 1.—A man, aged 26, complained of recurring, almost daily, attacks of pain in the right lower quadrant of the abdomen, associated with diarrhea. Examination revealed apical tuberculosis and tenderness in the right lower quadrant. Appendectomy was performed, and the patient recovered. The pathologic report showed an ulcerative type of tuberculosis of the appendix. The patient was readmitted to the hospital seven months later with generalized anasarca and died seventeen days later. Postmortem examination revealed general edema, hydrothorax, ascites, thrombosis of the right internal jugular and subclavian veins, chronic adhesive pericarditis with marked dilatation of the right ventricle and tuberculosis of the intestines and the apexes of the lungs.

Case 2.—A woman, aged 29, complained of attacks of pain in the right lower quadrant of the abdomen. Active pulmonary tuberculosis was present, with positive sputum. There were tenderness and rigidity in the right lower quadrant. Pararotomy revealed that both the cecum and the appendix were markedly thickened and surrounded by closely adherent omentum. The appendix was removed, and the patient made an uneventful recovery. The pathologic report showed an ulcerative type of tuberculosis of the appendix.

Case 3 (from St. Joseph's Hospital).—A man, aged 37, complained of pain in the right lower quadrant of the abdomen. The family and personal history were negative for tuberculosis. Laparotomy revealed a long appendix, which was hard and stiff, and numerous granulations scattered over the area. The cecum was normal. The patient recovered. The pathologic report was: hyperplastic tuberculosis of the appendix.

Beck (1920)[14].—A woman, aged 22, complained of general weakness and loss of weight. Examination revealed a normal heart and normal lungs. There was nothing abnormal in the abdomen, but vaginal examination revealed salpingo-oophoritis, which was diagnosed as tuberculosis of the adnexa. Laparotomy revealed that the middle portion of the appendix had sloughed out. There were tubercles over the tip of the appendix and on the tubes and ovaries, which were involved secondarily. The appendix and adnexa were removed. The patient recovered rapidly under roentgen treatment. The pathologic report was: tuberculosis of the appendix and adnexa.

Noehren and Mueller (1922)[5].—A woman, aged 31, with active pulmonary tuberculosis, complained of pain in the right lower quadrant of the abdomen. Examination revealed tenderness and a mass in the right lower quadrant. Laparotomy revealed a swollen, congested appendix, with some injection of the surrounding peritoneum. No signs of tuberculosis were visible grossly in the intestines, cecum and peritoneum. The tubes and ovaries were normal. The appendix was removed.

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12. Gatewood, G.: S. Clin., Chicago **4**:809, 1920.
13. Warwick, M.: Ann. Surg. **71**:139, 1920.
14. Beck, C.: S. Clin., Chicago **4**:1263, 1920.

The patient made an uneventful recovery and was discharged on the ninth day following the operation. The pathologic report was: tuberculosis of the appendix, with acute exacerbation.

Perrin and Dunet (1922)[15].—A girl, aged 15½ years, complained of pain in the right lower quadrant of the abdomen. There was no history of tuberculosis in the family. Examination revealed tenderness in the right lower quadrant, with some voluntary rigidity. Pelvic examination revealed a mass in the right side. Laparotomy revealed a short, very wide appendix. The other abdominal contents were normal. The appendix was removed. Recovery was uneventful. The pathologic report was: hyperplastic tuberculosis of the appendix, with acute inflammation and abscess formation.

Razzaboni (1925)[16].—Case 1.—A youth, aged 17, complained of abdominal cramps and alternating periods of constipation and diarrhea Examination of the lungs revealed tuberculosis; the abdomen was distended and fluid was palpable. A diagnosis of tuberculous peritonitis with ascites was made. Laparotomy revealed a large amount of fluid. A mass was found in the lower part of the abdomen on the right, made up of the cecum and appendix covered with tubercles. The appendix was 10 cm. long and felt hard. The author was sure that this was a hyperplastic type of tuberculosis of the appendix. The abdomen was closed in layers without removal of the appendix, and the patient made an uneventful recovery.

Case 2.—A man, aged 38, complained of a mass in the lower part of the abdomen on the right, which was becoming rapidly larger. Examination revealed apical tuberculosis on the left side. The abdomen was enlarged, and there was a large inguinoscrotal hernia on the right side. A diagnosis of tuberculous peritonitis, with concomitant right inguinoscrotal hernia, was made. Laparotomy revealed a large hernial sac containing the small intestine, cecum and appendix covered with tubercles. The appendix was thick and firm, and Razzaboni believed the condition to be due to a hyperplastic tuberculous process. A Bassini operation was performed, and the patient was discharged after spending a short time in the hospital. Shortly after, tuberculous meningitis developed, and the patient died. Permission for necropsy was not obtained.

Coley (1928)[17].—A man, aged 23, complained of pain in the right lower quadrant of the abdomen, of four months' duration. Examination revealed apical tuberculosis on the right and tenderness, rigidity and a palpable mass in the right lower quadrant of the abdomen. Laparatomy revealed a mass consisting of the cecum, appendix and omentum and enclosing an abscess cavity containing 1½ ounces (15.6 Gm.) of pus. The appendix was thickened and covered with fibrin. Near the cavity a pouchlike diverticulum of the terminal ileum was found, the distal portion of which had a hemorrhagic appearance. The remainder of the abdomen was normal. The appendix and diverticulum were removed, and the abdomen was drained. The pathologic diagnosis was: tuberculosis of the appendix, with acute suppurative periappendicitis and tuberculous diverticulum of the ileum. The patient was transferred to the ward for tuberculosis on the twenty-first day and died of pulmonary and enteric tuberculosis two months after operation.

Corvese (1925)[18].—A woman, aged 21, complained of amenorrhea, but examination resulted in a tentative diagnosis of tuberculous peritonitis. About five months

15. Perrin, E., and Dunet, C.: Presse méd. **30**:809, 1922.

16. Razzaboni, G.: Riforma med. **41**:965, 1925.

17. Coley, B. L.: Tuberculosis of Meckel's Diverticulum Associated with Tuberculous Appendix, Arch. Surg. **11**:519 (Oct.) 1925.

18. Corvese, A.: Rhode Island M. J. **8**:125, 1925.

later she had an attack of abdominal pain. Examination revealed tenderness and rigidity in the right lower quadrant of the abdomen, with marked distention. Laparotomy revealed a large amount of serous fluid in the abdomen; the appendix was gangrenous and adherent and had an abscess at its base. Appendectomy was performed, and drainage was instituted. The patient was discharged on the fifteenth day but drainage continued for seven months. The appendix was tuberculous, with an acute superimposed inflammation.

Popper (1926) [19].—A youth, aged 20, who suffered from pulmonary tuberculosis, complained of abdominal pain which came and went and which at times was severe. Examination revealed a tender mass near the umbilicus. Laparotomy revealed a long appendix covered with fibrin and some congestion of the cecum. There was no evidence of pathologic changes in the rest of the abdomen. The patient made an uneventful recovery. The pathologic report was: tuberculosis of the appendix, with superimposed acute inflammation.

Vergely (1927) [20].—A woman, four months pregnant, complained of pain in the epigastrium after meals and vomiting. Roentgen examination showed deformity of the pyloric cap. Consultation resulted in a diagnosis of pyloric ulceration, with possible appendicitis. She was given medical treatment to allay the attacks. Five months later she gave birth to a normal female child. About two months later laparotomy was performed. All the abdominal viscera were normal except the appendicular and cecal serosa, which were seeded with tubercles. The appendix was removed. The patient recovered. She had had an infiltration of the apex of the left lung during the pregnancy and shortly after the operation, but this had completely disappeared three months after the operation. Microscopic examination confirmed the tuberculous condition of the appendix.

Molfino (1927) [21].—A girl, aged 17, complained of repeated attacks of pain in the abdomen, which were localized in the right lower quadrant. Laparotomy was performed in May, 1926, and nothing abnormal was found. She continued to have attacks of pain, and a diagnosis of adnexal disease was made. Five months after operation, examination revealed large tender adnexa on the right side. Laparotomy at this time disclosed tuberculosis of the fallopian tubes, ovaries, cecum, terminal part of the ileum and the appendix. Both fallopian tubes and the right ovary were removed. The appendix was not removed, because of the dense adhesions binding it down closely to the cecum. The patient made an uneventful recovery. The pathologic report on the fallopian tubes and right ovary showed tuberculous infection.

Perera (1927) [22].—A girl, aged 19, complained of abdominal pain which recurred at irregular intervals. Examination revealed chronic pulmonary congestion and a tender mass over the appendix. Laparotomy revealed a large, thick but short appendix, with tuberculous granulations. The appendix was removed. The patient recovered and was well two years later.

Pfeiffer and Smyth (1928) [23].—A woman, aged 26, complained of marked diarrhea and loss of weight. There was a history of pulmonary tuberculosis, which had never been very active. Examination led to a diagnosis of colitis of unknown

19. Popper, H.: Wien. med. Wchnschr. **79**:478, 1929.

20. Vergely, J.: J. de méd. de Bordeaux **57**:20, 1927.

21. Molfino, A. H.: Semana méd. **1**:1534, 1927.

22. Perera, A.: Med. ibera **2**:125, 1927.

23. Pfeiffer, D. B., and Smyth, C. M., Jr.: S. Clin. North America **8**:877, 1928.

origin. Cecostomy was performed through a McBurney incision. The appendix was found to be red, thick and studded with tubercles, and a small amount of clear straw-colored fluid was found in the abdomen. There was also a mass about the size of a small lemon in the cecum near the base of the appendix. The appendix was removed. The pathologic report was tuberculosis. Postoperatively the patient was treated with irrigations of silver nitrate through a catheter sewed into the cecum. She also had treatment with ultraviolet rays and general care for eighteen months. She gained 45 pounds (20.4 Kg.), her weight increasing from 60 to 105 pounds (from 27.2 to 47.6 Kg.). Closure of the cecum was performed. No evidence of tuberculosis was found intra-abdominally, and the mass in the cecum had disappeared. The patient made an uneventful recovery.

Vargas (1929)[24].—A boy, aged 11 years, complained of attacks of pain in the right lower quadrant of the abdomen. These attacks recurred several times until he had a very severe attack, and he was brought to the hospital. The Pirquet reaction was positive. Laparotomy revealed an appendix studded with tubercles and bound down to the cecum. There was inflammation of the appendix, which also involved the cecum. No lesions of the intestines or peritoneum were found. The patient made an uneventful recovery. The pathologic report was tuberculosis of the appendix.

Askey (1929)[25].—A man, aged 27, complained of sudden pain in the lower part of the abdomen on the right, accompanied by nausea. Three days later, on seeing a physician, he was told that the condition was appendicitis. He continued to have pain in the right side for the next two months. At the end of this time examination revealed a tender, movable mass in the right lower quadrant. Laparotomy revealed a swollen appendix, with a small perforation near the base through which a grass stalk protruded. The cecum and the rest of the abdomen were normal. The patient made an uneventful recovery. The pathologic report was: tuberculosis of the appendix. Examination showed a normal heart and normal lungs.

Bloch and Mayer (1929) [26].—A woman, aged 31, complained of sterility and scanty menstrual periods for the past two years. Examination revealed a retroverted uterus. Laparotomy revealed miliary tubercles covering the adnexa, the ileocecal region and the appendix. The peritoneum and the rest of the abdomen were normal. The appendix was removed. The postoperative course was uneventful. The physician did not remove the involved adnexa because he believed that the seat of the tuberculous process was already in the abdomen and that the operation might disseminate the bacilli or cause the process to flare up.

P. Muller (1929) [27].—A woman, aged 25, complained of recurring attacks of pain, which were especially marked in the right lower quadrant of the abdomen. Examination of the chest gave negative findings. There was tenderness on the right side of the abdomen. Pelvic examination revealed tender, slightly enlarged adnexa. Laparotomy showed adhesions of the uterus to the sigmoid and rectum. The ovaries were adherent to the broad ligament and the pelvic brim. The appendix was atrophied at the tip and broad at the base. Hysterectomy and appendectomy were performed. The pathologic report was: tuberculosis of the adnexa and appendix. The patient made an uneventful recovery.

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24. Vargas, M.: Vida nueva **23**:207, 1929.
25. Askey, J. M.: California & West. Med. **30**:46, 1929.
26. Bloch, J. C., and Mayer, M.: Bull. Soc. d'obst. et de gynéc. **18**:321, 1929.
27. Muller, P.: Bull. et Soc. de chir. de Paris **21**:259, 1929.

Mason (1929)[28].—A man, aged 23, complained of pains in the lower part of the abdomen on the right and vomiting. Examination revealed pulmonary tuberculosis and tenderness in the right lower quadrant of the abdomen. Laparotomy revealed a long coiled and inflamed appendix, which was removed. The remainder of the abdomen was normal, except for enlarged lymphatic glands at the ileocecal angle. Pathologic examination revealed tuberculous appendicitis, with acute inflammation. The patient was later transferred to a sanatorium.

de Almeida Prado (1930)[29].—A youth, aged 18, was admitted to the hospital, complaining of pain in the abdomen, rectal tenderness and loss of weight. Examination revealed that the heart and lungs were normal; the abdomen was distended and tender. Roentgen examination revealed adhesions between the sigmoid and the appendix. Laparotomy revealed chronic tuberculous appendicitis and cicatricial mesosigmoiditis. Postoperatively the patient was given general treatment and ultraviolet irradiation.

Robles (1930)[30].—A girl, aged 17, who suffered from pulmonary tuberculosis and who was being treated by artificial pneumothorax, complained of severe pain in the right side of the abdomen. Appendectomy was performed. She made an uneventful recovery and was discharged from the hospital within eleven days. The pathologic report was: tuberculosis of the appendix.

Carnelli (1931)[31].—A man, aged 27, complained of pain in the abdomen, with alternating periods of constipation and diarrhea. Examination of the chest gave normal findings. The abdomen was distended and was tender and rigid on the right side, with a suggestion of a mass. Laparotomy revealed a long, inflamed appendix studded with tubercles, with free fluid in the peritoneal cavity. The rest of the abdomen showed no abnormality. The appendix was removed. Recovery was uneventful, and the patient was well after three years. The pathologic report was: primary hypertrophic tuberculosis of the appendix.

Stiles (1931)[32].—A youth, aged 19, complained of pain in the right lower quadrant of the abdomen, with nausea, which began two days prior to admission to the hospital. Examination revealed tenderness, rigidity and a palpable mass in the right lower quadrant. Laparotomy revealed an inflammatory mass on the right side, made up of omentum wrapped around the inflamed cecum. The appendix was not visualized. Resection of the entire ileocecal region and ileocolic anastomosis were performed. The postoperative course was uneventful. The pathologic report indicated hyperplastic tuberculosis of the appendix and cecum. Roentgen examination of the chest gave negative findings for tuberculosis.

Sanguily Quintana (1931)[33].—A woman, aged 29, complained of a sensation of heaviness in the abdomen, difficult defecation, leukorrhea and loss of weight. Examination of the apex of the left lung revealed tuberculosis and a distended tender abdomen. Pain was especially marked over McBurney's point. Pelvic examination revealed a retroverted uterus and tender adnexa. Laparotomy was performed, and a Baldy-Webster suspension of the uterus was done, as well as salpingectomy and appendectomy. Pathologic examination showed tuberculous appendicitis.

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28. Mason, G. A.: Newcastle M. J. **9**:122, 1929.
29. de Almeida Prado, A.: Ann. Fac. de med. de São Paulo **5**:311, 1930.
30. Robles, A. A.: Rev. Soc. de med. int. y Soc. de tisiol. **6**:577, 1930.
31. Carnelli, R.: Arch. ital. di chir. **30**:158, 1931.
32. Stiles, C. D., Jr.: South. M. J. **24**:958, 1931.
33. Sanguily Quintana, J.: Vida nueva **28**:209, 1931.

Finzi (1932)[34].—A man, aged 24, was operated on for appendicitis in August, 1927. The postoperative course was uneventful. Two years later the patient returned with a palpable mass in the right side of the abdomen. Laparotomy revealed ileocecal tuberculosis. Ileocecocolic resection and lateral ileotransversostomy were performed. The patient made an uneventful recovery. Pathologic examination confirmed the diagnosis of ileocecal tuberculosis, and on careful study of the appendix removed two years previously hypertrophic tuberculosis was found.

Primary tuberculosis of the appendix must be very rare. While its existence cannot be denied theoretically, so far as we know, there is only 1 case on record (Beck[14]) in which, after the patient died subsequent to removal of a tuberculous appendix, autopsy failed to reveal any other tuberculous lesion, with exception of involvement of the lymph nodes in the ileocecal region. However, a latent microscopic or old healed focus or a microscopic lesion in the lymph nodes might have been overlooked. In this connection, an appendix removed either as a routine or by design and found to be tuberculous only after microscopic examination may afford the first information as to the presence of this disease in the body and the patient subsequently may show other lesions. With this in mind, the following case is offered:

Koster Clinic.—CASE 1.—E. H., a woman, aged 23, was admitted to the hospital on Oct. 9, 1931, complaining of pain in the lower right quadrant of the abdomen.

Six years before admission she began to have dull pains in the right lower quadrant of the abdomen. These pains were intermittent but not severe and continued until two weeks before admission, when they began to be severe and cramplike. They radiated to the lower part of the back and the right thigh and were aggravated if the patient walked or rested her weight on the right side. The patient also had a white, watery vaginal discharge and nausea when these pains became more severe. Menstruation had been regular; the patient had begun to menstruate at the age of 13; the periods occurred every twenty-eight days and lasted four days. Three months before admission a physician inserted a hard rubber pessary for the retroversion of the uterus. The past history and family history were negative. The patient was not married.

Physical examination revealed a young white adult female, well nourished and well developed, who did not appear acutely ill. The head and neck were normal. There was equal expansion on both sides of the chest, the lungs were clear, and the breath sounds were normal. The heart sounds were regular, and there were no murmurs.

There was some tenderness in the right lower quadrant of the abdomen, especially over McBurney's point, radiating to the epigastrium. There was slight tenderness in the left lower quadrant. No spasticity or masses were palpable in the abdomen. Murphy's sign was absent. The extremities and the reflexes were normal.

Rectal examination revealed a retroverted uterus and some tenderness on the right side. No masses were palpable. The temperature was 99 F.; the pulse rate was 90 and the respiratory rate 22 per minute.

The laboratory reported that the urine showed a trace of albumin, but no sugar, and a few white blood cells microscopically. The hemoglobin was 82 per cent.

34. Finzi, O.: Boll. e mem. Soc. piemontese di chir. **2**:986, 1932.

The red blood cells numbered 4,300,000 per cubic millimeter; the white blood cells, 10,800, with 70 per cent polymorphonuclears, 16 per cent lymphocytes and 12 per cent monocytes.

A diagnosis of chronic appendicitis and retroverted uterus was made.

The next day laparotomy was performed under spinal anesthesia. The liver was ptosed to the level of the umbilicus; the gallbladder and stomach appeared normal. The uterus was retroverted, and the appendix, which was bulbous, was bound down by firm adhesions to the cecum. There were a few fine adhesions in the posterior culdesac; these were cut. A Simpson-Gilliam suspension of the uterus and appendectomy were performed. The abdomen was closed in layers.

The patient made an uneventful recovery. Microscopic examination of the appendix showed tuberculosis. Roentgenologic study of the chest revealed no signs of tuberculosis. The patient was discharged on October 21.

From an operative and clinical standpoint, this case is one of primary tuberculosis of the appendix. To the time of writing the patient has not presented any other evidence of a tuberculous lesion. Beck,[14] in 1920, reported a case of tuberculosis of the appendix with extension to the fallopian tubes and the ovaries, in which there were no other abdominal or pulmonary signs of tuberculosis. He reported this case as one of primary tuberculosis of the appendix.

The following two cases are clinically typical of acute appendicitis:

Case 2.—M. A., a girl, aged 17, was admitted to the hospital on June 26, 1931, complaining of pain in the lower part of the abdomen on the right and nausea.

The illness began three days prior to admission, when she was seized with generalized abdominal cramps. She was nauseated at the time of admission but did not vomit. About twenty-four hours after the onset the pain became localized in the lower part of the abdomen on the right.

The family history was negative, except that the brother of the patient's father had active pulmonary tuberculosis. The patient had had scarlet fever, measles, whooping cough and influenza. Tonsillectomy was performed in 1926. Menstruation began at the age of 13; the periods occurred every twenty-eight days and lasted three days.

The patient appeared acutely ill. The chest showed equal expansion on both sides. The breath sounds were normal, and no râles were heard. The heart sounds were regular, with no murmurs. There were tenderness and rigidity in the entire lower part of the abdomen; these were more marked in the right lower quadrant. Tenderness on release of pressure in the left lower quadrant was referred to the right lower quadrant. Murphy's sign was absent.

Rectal examination revealed a tender mass high on the right side.

Examination of the urine gave negative results. The red blood cells numbered 4,000,000 per cubic millimeter, with hemoglobin 86 per cent. The white blood cells totaled 13,400, with 84 per cent polymorphonuclears and 16 per cent lymphocytes.

A diagnosis of appendicular abscess was made. Laparotomy was performed under spinal anesthesia. An acutely inflamed abscessed appendix was found walled off by omentum and by the cecum and ileum. The diameter of the appendix at the base was 1⅛ inches (2.8 cm.), while the length was 3 inches (7.6 cm.). Appendectomy was performed. A cigaret drain was inserted to the pelvis, and the abdomen was closed in layers.

The patient made an uneventful recovery. The wound drained profusely for about nine days, then healed rapidly.

The pathologic report was: tuberculosis of the appendix, with acute purulent inflammation. A roentgenologic study of the chest revealed no signs of tuberculosis. The patient was discharged on July 12.

Askey,[25] in 1929, reported a case in which a diagnosis of appendicular abscess was made. Laparotomy revealed a walled-off appendicular abscess with a perforation at the tip containing a grass stalk. Microscopic examination revealed tuberculosis of the appendix.

Similarly, in our case we had no idea that we were dealing with primary tuberculosis of the appendix until microscopic examination revealed it. The next case reported is similar:

Case 3.—J. R., a boy, aged 14, was admitted to the hospital on Sept. 27, 1930, complaining of pain in the lower part of the abdomen on the right, with nausea and vomiting.

The illness began the day before admission, when the patient was suddenly seized with generalized abdominal cramps. He also became nauseated and vomited three times. The same night the pain became localized in the right lower part of the abdomen.

The family history was negative. The patient had measles when he was 6 years old. He stated that he had had some uneasiness in the lower part of the abdomen on the right during the month prior to admission. He appeared to be acutely ill. The chest revealed equal expansion on both sides. The lungs were clear, and no abnormal sounds were heard. The heart sounds were regular, and there were no murmurs.

There were tenderness and rigidity in the right lower quadrant of the abdomen. No tenderness on rebound was present. There was no Murphy's sign. Rectal examination gave negative results, except for some tenderness on the right side. The extremities and the reflexes were normal. The temperature was 100 F.; the pulse rate was 112 and the respiratory rate 20 per minute. Examination of the urine gave negative results.

The red blood cell count was 4,600,000, with hemoglobin 92 per cent. The white blood cells totaled 14,000, with 82 per cent polymorphonuclears and 18 per cent lymphocytes.

A diagnosis of acute appendicitis was made. Laparotomy was performed under spinal anesthesia; it revealed acute suppurative appendicitis. The appendix was bound down by adhesions to the cecum and covered by lightly adherent omentum. Appendectomy was performed. The postoperative course was uneventful. The temperature, pulse rate and respirations were normal within forty-eight hours after operation and remained so until the patient's discharge from the hospital on October 8. A few days prior to his discharge, following a pathologic report of tuberculosis of the appendix, roentgenologic study of the chest revealed no pulmonary involvement.

Since in cases 2 and 3 there was no clinical or roentgenographic evidence of tuberculosis nor any signs of tuberculosis within the peritoneal cavity visible to the surgeon, the condition in both these cases might be considered, from a clinical standpoint at least, as primary appendicular tuberculosis, bearing in mind that at some future date a lesion may appear that was not demonstrable at the time of writing.

The fourth case is one of frank pulmonary tuberculosis complicated by tuberculosis of the appendix.

CASE 4.—H. L., aged 31, was admitted to the hospital on May 30, 1930, complaining of pain in the right lower quadrant of the abdomen. Three weeks prior to admission he began to have sharp cramplike pains in the lower part of the abdomen on the right, which did not radiate anywhere but remained localized in that area. The pains became worse until the day of admission, when they were so severe that the patient was unable to walk.

The chest presented equal expansion on both sides. The breath sounds in both apexes were bronchovesicular, and a few subcrepitant râles were heard. The heart beat was regular, and no murmurs were present. There was tenderness in the right lower quadrant of the abdomen, which was more marked over McBurney's point. There was no rigidity and no mass was palpable. Murphy and psoas signs were not present. No tenderness on release of pressure was present. Rectal examination gave negative results. The temperature was 99 F.; the pulse rate was 98 and the respiratory rate 20 per minute.

Laboratory reports revealed negative results of urinalysis, except for a faint trace of albumin. The red blood cell count was 5,450,000, with hemoglobin 100 per cent. There were 10,150 white blood cells, with 72 per cent polymorphonuclears, 24 per cent lymphocytes and 4 per cent monocytes.

A diagnosis of subacute appendicitis and pulmonary tuberculosis was made.

Laparotomy was performed under spinal anesthesia. An acutely inflamed appendix was found bound down to the lateral pelvic wall by firm adhesions and covered with omentum. The ileum was loosely adherent to the base of the appendix. The other abdominal viscera appeared normal. Appendectomy was performed without drainage. On the second postoperative day the patient began to cough up a frothy, blood-stained sputum. His temperature was 100.4 F.; the pulse rate was 96 and the respiratory rate 22 per minute. Examination of the chest revealed dulness in the apex of both lungs and fine subcrepitant râles. Both bases were clear. The next day the patient had typical prune juice sputum and was coughing moderately. His temperature rose to 102.2 F., with a pulse rate of 120, but respirations remained at 22 per minute. The sputum was negative for tubercle bacilli.

The patient's condition seemed fair until the ninth day after the operation, when he coughed so hard that his wound opened and a small loop of ileum was eviscerated. This was replaced in the abdomen, and the wound was tightly strapped with adhesive tape. The next day the patient's condition appeared to be poor. Examination of the chest revealed many moist râles, with bronchial and bronchovesicular breathing from the apex to the base of the lung on the right side and from the apex to the inferior angle of the scapula on the left.

The base of the left lung showed flatness and absence of breath and voice sounds—all evidence of effusion. The heart was enlarged to the left about 1 cm. outside the midclavicular line. The sounds were of poor quality. Examination of the sputum showed Bacillus tuberculosis. Unquestionably, the pulmonary lesion at this time was acute tuberculous pneumonia. The patient's condition became progressively worse, and death occurred on July 12 at 1:50 p. m.

The pathologic report on the condition of the appendix was: "caseating tuberculosis."

COMMENT

From a pathologic standpoint, the lesions confined to the appendix may be divided into two types: (1) the ulcerative and (2) the hyperplastic. The former is by far the more common. Grossly, the appearance of the appendix may vary from that of a seemingly normal organ with perhaps slight congestion of the superficial capillaries to that of an organ showing all the signs of actively acute inflammation. The walls may be slightly thickened, and the serosa may show small tubercles or even a thin plastic exudate on the surface. Gross ulceration of the mucosa may occur, resulting in a greater or lesser loss of substance.

Fig. 1.—Section of the wall of the appendix with a thin mucosa without folds. The serosa is slightly thickened. There are some adhesions, which show some nodular aggregation of granulation tissue with a lighter center. Low power magnification.

The base of an ulceration may show extensive caseous material. In other cases the floor of the ulcer may show minute grayish tubercles. The ulceration of the mucosa may extend into and through the submucosa and in some instances even through the muscular coat to such an extent that nothing may be left of the latter, the remainder of the wall being only serosa. In the event that attempts at healing are successful, the ulcerative surfaces become adherent, and the organ becomes either strictured or obliterated. Microscopically, the mucosa and submucosa show the most extensive involvement, although, as has been said

before, the musculature may also suffer considerably, the lesion appearing in the form of discrete tubercles or extensive ulcerations and necrosis, with the characteristic epithelioid and giant cells around an area of caseation. In the earlier stages the ulceration is more likely to occur either at the tip or at the base of the organ. If the ulceration becomes advanced it may even extend through the serosa, with resultant perforation, following which any of the sequelae of perforative appendicitis may develop.

The hyperplastic type of tuberculous appendicitis is much more rare. It is characterized by a very large appendix with a thickened wall,

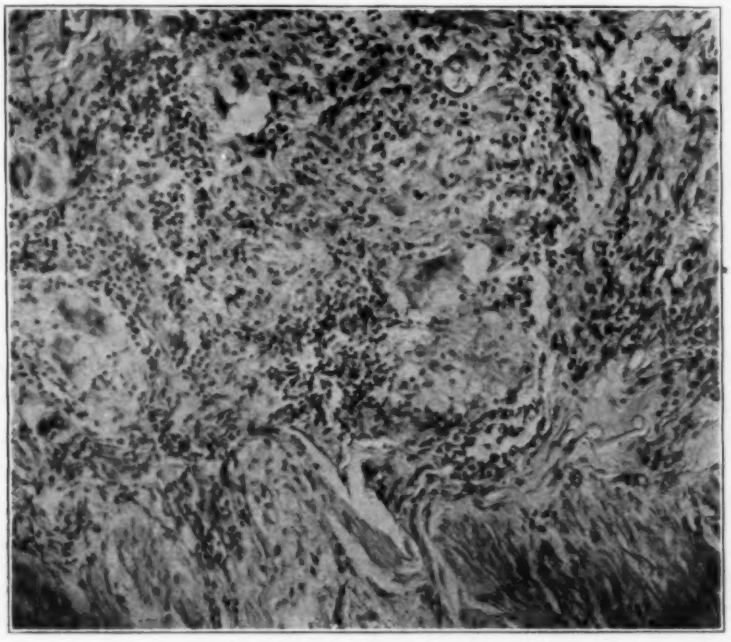

Fig. 2.—Serosa of the appendix, showing granulation tissue extending slightly to the outer muscular coat. The granulation tissue encloses groups of epithelioid cells and several giant cells of the Langerhans type.

marked proliferation of connective tissue and complete or relative absence of caseation. The walls become markedly increased in thickness, and occasionally the organ may become so large as to be palpable through the abdominal wall, in which event it may be mistaken for a neoplasm. The hyperplasia of the connective tissue and the contraction which it undergoes may not be entirely uniform, causing irregularities in the shape of the organ. The walls become rigid, and the lumen may show a tendency toward obliteration. While, on superficial examination it may be mistaken for a neoplasm, the differentiation should not be difficult on close inspection.

On microscopic examination, the mucosa is usually found to be intact. Instead of being destructive as in the ulcerative type, the lesion is, as the name implies, a hyperplastic one, consisting most frequently in marked thickening of the muscular coat as a result of a deposition of large amounts of connective tissue and lymphoid infiltration. The submucosa may show some tubercles, but on the whole the typical picture is one of lack of ulceration and caseation, with a large amount of connective tissue reaction.

The secondary form of tuberculosis of the appendix is frequently associated with a tuberculous lesion of the intestines, particularly of the

Fig. 3.—Hyperplastic mucosa with large follicles and unusually large secondary follicles. The submucosa and part of the muscularis is substituted by granulation tissue. There are numerous nodules which consist of epithelioid cells and which stain lighter than the adjacent area infiltrated with round cells.

cecum. Some authors, including Mayo, have gone so far as to state that it is practically always associated with the same infection in the latter. Then, too, most observers have had the experience of finding ileocecal or intestinal tuberculosis frequently, with no involvement of the appendix. These two findings suggest that the appendix is usually secondarily infected. It must be remembered, however, that whether the local infection occurs by extension or by the hematogenous route, the bacilli may be disseminated along the alimentary tract in many

places, with many foci developing simultaneously and yet with different degrees of rapidity. In addition to the obvious method of entrance of tubercle bacilli into the intestinal tract by the swallowing of contaminated sputum, there is also the possibility of the entrance of the organism in contaminated food. This includes not only infected milk but also infected butter and cheese. The latter type of infection is one explanation for the possible occurrence of primary tuberculosis (Schroeder and Cotton [35]). Regarding the other means by which the appendix may become infected, namely, by way of the peritoneum, the lymph stream and the blood stream, little can be said. That infection by such routes is theoretically possible cannot be denied, but evidence in favor of the transmission of the bacilli by these routes is not strong.

Clinically, the disease may manifest itself in two forms, the acute and the chronic. In the acute form differentiation from acute appendicitis of the ordinary variety is almost impossible. It may, of course, be suspected when the syndrome of acute appendicitis occurs in a patient who already has well developed tuberculous lesions elsewhere in the body, but in the absence of such a history there are no signs by means of which the tuberculous type of acute appendicitis can be differentiated from any other form. In the chronic form, which is far more frequently encountered, tuberculosis elsewhere in the body, a history of occasional attacks of diarrhea, the recognition of a mass in the region of the appendix without symptoms of abscess and, in children, hard muscular tumors in the abdomen which are not fecal masses are all signs which, in the presence of the ordinary symptoms of chronic appendicitis, might point to the tuberculous nature of the lesion. One other form of tuberculosis of the appendix is encountered clinically, namely, the latent form, in which the appendix which has been removed as a routine during the course of some other operation is found to be tuberculous on histologic examination. This type may never cause any symptoms.

White,[36] in a series of autopsies, noted several instances of acute and chronic tuberculous disease of the appendix in persons who had never shown any signs of appendicular disease during life. The general signs of the chronic variety of tuberculous appendicitis include a characteristic rise in temperature in the afternoon, with slight acceleration of the pulse rate, perhaps slight loss of weight and, in some instances, nocturnal perspiration. The chronicity is extreme, but there may be interruptions of acute exacerbations. Between these acute flare-ups there is a vague sense of discomfort in the right lower quadrant of the abdomen, with some tenderness. The clinical diagnosis should be suggested in the face of a history of chronic appendicitis with which there is associated a progressive loss of weight, rise in temperature in the

35. Schroeder, E. C., and Cotton, W. E., quoted by Eisendrath.[9]

36. White, J.: Ann. Rep. Henry Phipps Institute, 1906-1907 and 1907-1908.

afternoon, nocturnal perspiration and occasional attacks of diarrhea. The literature since Muller's [3] article contains little of value regarding the prognosis in tuberculous appendicitis. In only 8 of the 66 cases which he reviewed was it reported definitely that the patient was cured, but the report of these cures is of little value since the patients were followed for only a few months after operation. Muller noted that in 3 cases, one, two and three years, respectively, elapsed before death occurred from pulmonary tuberculosis. Ten patients were recorded as still suffering from some form of tuberculosis at the time of the report. One patient is said to have died as a direct result of the operation. Fifteen others died a short time after operation, and the final result is not stated in the remaining cases. If the disease is primary and if the operation is performed before secondary involvement occurs, there should be hope of a cure. Secondary tuberculosis of the appendix offers a poorer prognosis, especially when following pulmonary involvement and in the presence of a coincidental lesion. However, in one of Pauchet's [37] cases, in which the appendix was removed because of pain over the region, at which time the peritoneum was found to be studded with tubercles and the appendix also involved, laparotomy for incisional hernia performed some time later revealed a normal appearance of the peritoneum.

Pfeiffer and Smyth's [23] case, which is abstracted in this article, also showed complete disappearance of tuberculous lesions in the abdomen eighteen months after appendectomy and cecostomy at the time when the cecostomy opening was closed.

Regarding the treatment, little need be said. If the condition is acute, the appendix should be removed immediately, even in the presence of complicating pulmonary disease, under some form of anesthesia other than inhalation narcosis. The anesthesia of choice is the spinal. In the chronic type of the disease the condition of the lungs should determine the advisability of surgical intervention.

SUMMARY AND CONCLUSION

Up to December, 1917, 89 cases of tuberculosis of the appendix had been reported in the literature by Scott.[4] Three other cases before 1917 that were not included in the report are given in this article, followed by a complete abstract of 31 authentic cases reported from 1917 to the time of writing. To this number we have added 4 cases of our own which we found in 3,271 consecutive appendectomies. In 3 of our cases the condition was apparently primary tuberculosis of the appendix; in the fourth there was coexisting pulmonary tuberculosis. This article brings the total number of authentic cases of tuberculous appendixes reported in the literature to the end of 1932 up to 127.

37. Pauchet, quoted by Petit, M.: Thèse de Paris, 1905, p. 71.

HEMORRHAGE AND SHOCK AS CAUSES OF DEATH FOLLOWING ACUTE PORTAL OBSTRUCTION

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ST. LOUIS

Although it has been known for nearly a century that acute obstruction of the portal vein, such as that produced by ligation or that occasionally occurring through thrombosis after biliary operations, is always followed in a short time by death, no satisfactory explanation of the fatal outcome has been offered. The first demonstration of the phenomenon is attributed to Oré,[1] who, in 1856, discovered that ligation of the portal vein in rabbits resulted in the death of the animals in a short time. It is interesting that Claude Bernard [2] at one time admitted a complete inability to offer an explanation, but several years later [3] expressed the theory that exsanguination, by stasis of blood in the intestinal tract, with a consequent fatal anemia might account for death. However, he offered no proof of that supposition, nor was he aware that Tappenheimer [4] had previously reported experiments which tended to disprove the idea.

In an effort to explain the cause of death following ligation of the portal vein we resorted to many different types of experiments.

EXPERIMENTAL PROCEDURES AND FINDINGS

Adult cats or dogs were anesthetized with ether or sodium amytal (about 75 mg. per kilogram of body weight, given intravenously), the abdomen was opened, and the portal vein was exposed at the hilus of the liver and ligated. Most of the animals were starved for from eighteen to twenty-four hours, but some were not. When blood pressure readings were taken, either the carotid or the femoral artery was connected with a mercury manometer and a continuous

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1. Oré, quoted by Neuhof.[5]

2. Bernard, Claude: Leçons sur les propriétés physiologiques et les altérations pathologiques des liquides de l'organisme, Paris, J. B. Baillière et fils, 1858, vol. 2, p. 196.

3. Bernard, Claude: Leçons sur le diabète et la glycogenèse animale, Paris, J. B. Baillière et fils, 1877, p. 316.

4. Tappenheimer, H.: Ueber den Zustand des Blutstroms nach Unterbindung der Pfortader, Arb. a. d. Physiol. Anstalt, Leipzig **7**:11, 1873.

tracing was obtained. Our experiments may best be described by considering them in separate groups:

1. *General Observations.*—The behavior of animals and the pathologic changes occurring as a result of ligation of the portal vein are constant and have been carefully described by Neuhof [5] and others. We observed few symptoms or signs which could not be explained on a basis of shock due to hemorrhage. The animal recovers slowly, if at all, from the effects of the anesthetic. If it regains consciousness, it appears to be desperately ill at all times and takes no interest in its surroundings. Extreme weakness is constantly observed; in fact it is so marked that the animal is compelled to maintain a recumbent position before it loses consciousness. The mucous membranes of the mouth are very pale. The pulse is of poor volume and tachycardia is usually present. Respiration may be variable, but the increased depth with rapid rate typical of air hunger resulting from hemorrhage is frequently seen. The blood pressure falls sharply within a

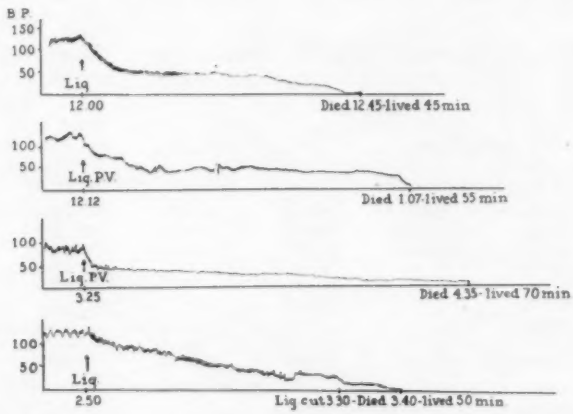

Chart 1.—Blood pressure tracings of four dogs following ligation *(Lig.)* of the portal vein *(P. V.)*, showing the sharp drop to "shock" level and death. In the lowest curve the ligature was cut in an effort to revive the animal, but this was done after irremediable changes had taken place.

few minutes after ligation and gradually decreases until death (chart 1). In a series of nineteen dogs on which portal ligation was performed the average duration of life was sixty-six minutes (table 1). The variations observed in the duration of life of starved or nonstarved animals, whether given ether or sodium amytal intravenously as an anesthetic, are so slight that they are probably of no significance. However, if the ligature is not placed high enough (i. e., proximally) to include the coronary and pancreaticoduodenal veins, or if the ligature is not absolutely tight, the duration of life may be prolonged considerably. At autopsy the spleen and the entire intestinal tract including the stomach, small bowel and large bowel are cyanotic, edematous and engorged with blood. The spleen is enlarged from three to six times. The serosa of the intestine loses its luster, but definite gangrene is not present. The wall of the intestine is firm

5. Neuhof, Harold: Experimental Ligation of the Portal Vein: Its Application to the Treatment of Suppurative Pylephlebitis, Surg., Gynec. & Obst. **16**:481, 1913.

and thickened and microscopically is filled with red blood cells. The omentum and mesentery are likewise edematous. Numerous superficial and deep hemorrhages are encountered in the organs mentioned. Occasionally small amounts of bloody fluid are found in the lumen of the stomach and intestine. Scott and Wangensteen[6] noted that there is a considerable loss of blood and fluid into long loops of intestine experimentally strangulated. In some instances this loss is of sufficient magnitude to cause death.

2. *Toxicity of the Blood and Lymph.*—In a series of six dogs the thoracic duct was dissected and intubated, and lymph was collected for a control period before ligation of the portal vein and then afterward until the animal died. Just before death, samples of systemic blood and blood from the portal vein behind the ligature were also collected. Clotting was prevented by the use of sodium oxalate (10 mg. to 10 cc.). The clear plasma was then injected into guinea-pigs and white mice intraperitoneally in doses up to 3 cc. per hundred grams of weight. Without describing in detail these experiments it was apparent

TABLE 1.—*Duration of Life Following Ligation of the Portal Vein*

	19 Dogs				6 Cats	
	Ether Anesthesia		Amytal Anesthesia		Ether Anesthesia	
	Starved	Not Starved	Starved	Not Starved	Starved	Not Starved
	90 min.	45 min.	95 min.	65 min.	60 min.	60 min.
	60 min.	60 min.	95 min.	30 min.	60 min.	
	60 min.	100 min.	45 min.	55 min.	35 min.	
	35 min.		35 min.		65 min.	
	55 min.		50 min.		60 min.	
	140 min.		35 min.			
	80 min.					
Average*	74 min.	68 min.	60 min.	57 min.	56 min.	60 min.

* The average for all the dogs was 66 minutes.

that none of the injected material proved toxic; and when it was, there was no essential difference over the controls.

3. *Increase in Weight of the Splanchnic Area.*—Another series of dogs and cats was operated on in pairs, one serving as a control, the other dying about one hour after ligation of the portal vein, at which time the control was killed. The entire gastro-intestinal tract was removed from each and weighed to determine how much blood was lost in the splanchnic area. These experiments have been reported previously,[7] and it need only be mentioned here that the increase in weight of the stomach, intestine and spleen in the animals with occlusion of the portal vein—due presumably to the entrapped blood—is great enough to account for the fatal outcome on the basis of loss of blood from the systemic circulation alone. Thus in the dogs this loss of blood, as shown by the increased weight of the gastro-intestinal tract, is 5.2 per cent of the body weight; in cats

6. Scott, H. G., and Wangensteen, O. H.: Blood Losses in Experimental Intestinal Strangulations and Their Relationship to Degree of Shock and Death, Proc. Soc. Exper. Biol. & Med. **29**:748, 1932.

7. Elman, Robert, and Cole, W. H.: Loss of Blood as a Factor in Death from Acute Portal Obstruction, Proc. Soc. Exper. Biol. & Med. **29**:1122, 1932.

it is 3.4 per cent. These figures exceed the amount of blood necessary to cause death by hemorrhage alone.[8]

4. *Effects of Transfusion.*—Efforts to combat loss of blood, or more correctly loss of fluid, after ligation of the portal vein almost always result in the prolongation of the life of the animal. As would be expected, the most efficient procedure is the transfusion of blood. For a limited time the intravenous injection of physiologic solution of sodium chloride is efficient in raising the low blood pressure. Injection of a solution of acacia produces a greater improvement, but the effect is poorly sustained. One must emphasize the fact, however, that even when transfusion of blood is used to combat the shock following the ligation it must be given before the animal becomes moribund. It is a fact well known in clinical experience that supportive measures to combat the shock of hemorrhage must be instituted shortly after shock ensues in order to prevent a high mortality. In the present experiments (table 2), for example, after ligation of the portal vein the average duration of life of six consecutive animals, which

TABLE 2.—*Effect of Transfusion of Blood on "Shock" Following Ligation of the Portal Vein*

	Number	Weight of Animal	Duration of Life	Amount of Blood, Cc.
Flow of blood not constant..	1	2.7 Kg.	2 hrs., 15 min.	275
	2	4.0 Kg.	2 hrs., 15 min.	350
	3	8.0 Kg.	3 hrs., 30 min.	850
	4	12.0 Kg.	3 hrs.*	1,100
	5	6.0 Kg.	1 hr.	200
	6	3.4 Kg.	2 hrs., 20 min.	450
Average duration of life, 2 hours, 23 minutes				
Flow constant, maintaining the blood pressure above the critical level of from 50 to 60 mm.	7	5.8 Kg.	7 hrs.*	1,050
	8	8.7 Kg.	3 hrs., 30 min.	1,490
	9	3.6 Kg.	5 hrs.	950
	10	5.4 Kg.	7 hrs., 30 min.*	1,250
Average duration of life, 6 hours, 15 minutes				

* The animal lived an unknown length of time beyond the figure specified.

were given a transfusion carelessly with an inconstant flow of blood, could be prolonged only to two hours and twenty-three minutes. We noted moreover, that if the blood pressure had been in the shock level for a half hour or more, and transfusion was neglected until the blood pressure fell below the critical level (say 40 mm. of mercury) even for a few minutes, we could not prevent death in spite of the transfusion of large quantities of blood. Similarly, if the ligature of the portal vein were cut too late, recovery could not occur (chart 1, lowest curve). Apparently certain vital organs such as the brain perhaps suffer irremediable damage after the blood pressure drops below a certain level even for a short time. On the other hand if the flow of blood during transfusion is maintained constantly, beginning fifteen or twenty minutes after ligation of the vein, thus preventing a fall of pressure below a critical level, life can be maintained for many hours (average, six hours and fifteen minutes +), as is illustrated by the last four consecutive animals in table 2. Two of these animals were still alive when last seen seven hours and seven hours and one-half, respec-

8. Johnson, G. S., and Blalock, A.: Experimental Shock: IX. Study of Effects of Loss of Whole Blood, of Blood Plasma and of Red Blood Cells, Arch. Surg. **22**:626 (April) 1931.

tively after the ligation. (This experiment is graphically represented in chart 2.) From the standpoint of these experiments it is of no particular interest how much longer than seven hours an animal will live following ligation of the portal vein, because by that time the factor of gangrene of the intestine enters as a complication. Invariably, when a considerable amount of blood is transfused into the animal following ligation of the portal vein, mucosal as well as serosal hemorrhages will occur and bloody fluid will be found in variable quantities in the lumen of the intestine and stomach and the peritoneal cavity. Quantities of bloody fluid will be passed by rectum. The rapid loss of blood in this manner, aided by the early effects of gangrene, probably explains the inability to keep these animals alive for twenty-four hours or longer. After intestinal hemorrhages are manifested to any considerable extent, death usually follows in a short time. Hemorrhage is probably aided by the fact that no tendencies to clotting are exhibited in the blood trapped behind the ligature. Tschernikoff [9] and his associates called attention to the delayed clotting time in the blood trapped in the portal system behind the ligature. In contrast, Krymholz [10] had previously noted a shortened clotting time of the systemic blood after ligation of the portal vein, especially as the animal approached death. Other observers [11] have noted similarly that following extensive hemorrhage the systemic blood

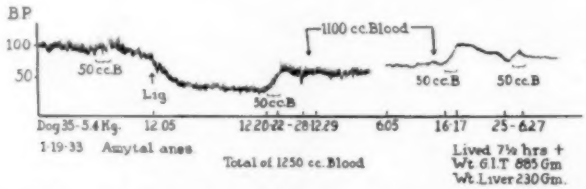

Chart 2.—Blood pressure tracing of one experiment mentioned in table 2. The usual fall in blood pressure is shown after ligation (*Lig.*) of the portal vein. Fifteen minutes later 50 cc. of blood was given, resulting in a sharp elevation. In all, 1,100 cc. of blood was given, with prolongation of life to over seven and a half hours. Compare this with the inevitable death in one hour when no transfusion is given (chart 1). *G.I.T.* indicates the gastro-intestinal tract.

clots much faster, and indeed it seems probable that the mechanism is the same in both cases. It appears to be a way nature has of aiding in "stopping the leak" by the formation of a clot more rapidly.

5. *Ligation of Splanchnic Arteries.*—When we discovered that the duration of life following ligation of the portal vein could be markedly increased by transfusion of blood, it seemed logical to assume that shock following ligation could be more readily prevented if at least some of the arteries supplying the portal system were ligated simultaneously with the portal vein. Accordingly, on two

9. Tschernikoff, A. M.; Malinjuk, W. W.; Jakubovitsch, M. I., and Klantaroff, M. C.: Zur Unterbindung der V. Portae, Arch. f. d. ges. Physiol. **227**:85, 1931.

10. Krymholz, M. L.: Experimenteller Beitrag zur Frage der Unterbindung der Pfortader (Einwirkung auf Druck und Gerinnungsvermögen des Blutes), Ztschr. f. d. ges. exper. Med. **67**:319, 1929.

11. Gray, H., and Lunt, L. K.: Factors Affecting the Coagulation Time of the Blood: V. The Effects of Hemorrhage, Am. J. Physiol. **34**:332, 1914.

occasions we ligated the superior mesenteric, inferior mesenteric, gastric and splenic arteries simultaneously with the portal vein. With transfusion of a small amount of blood one animal was alive when last seen at the end of six hours, and the other died at the end of six and one-half hours. The amount of blood required to maintain a blood pressure compatible with life was 15 and 16 cc. per kilogram of body weight per hour, respectively, which, as will be noted in table 2, is less than one half as much blood as that required by the last four animals, which were given transfusions after ligation of the portal vein alone. The last four dogs with ligation of the vein alone required as much as 26, 38, 52 and 32 cc. of blood per kilogram of body weight per hour. Since some of the animals lived longer than the six or seven hour period of observation, it might seem difficult to draw conclusions as to the speed of progression of "shock." This is of course a source of error, but was the same in each series of animals, since one half of each group lived beyond the final hour of observation. The marked difference in the amount of blood required must therefore be very significant. In other words, when a large portion of the systemic blood is

TABLE 3.—*Ligation of the Aorta Alone (Above the Celiac Axis) as Compared with Simultaneous Ligation of the Aorta with the Portal Vein*

	Dogs Duration of Life		Cats Duration of Life	
	Ligation of Aorta Alone	Ligation of Aorta with Portal Vein	Ligation of Aorta Alone	Ligation of Aorta with Portal Vein
	6 hrs.*	6 hrs.*	3 hrs., 5 min.	3 hrs., 35 min.
	3 hrs., 45 min.	4 hrs., 15 min.	4 hrs., 5 min.	4 hrs., 20 min.
	5 hrs., 15 min.	1 hr., 45 min.	6 hrs.	4 hrs., 15 min.
	3 hrs., 10 min.	5 hrs., 45 min.	6 hrs., 30 min.	4 hrs., 30 min.
		5 hrs.		
		3 hrs.		
Average	4 hrs., 32 min.	4 hrs., 18 min.	5 hrs.	4 hrs., 10 min.

* The animal lived an unknown length of time beyond the figure specified.

prevented from entering the portal system by ligation of some of the arteries supplying it, it is much easier to keep the animal alive after ligation of the portal vein. This appears to be added evidence that the shock is due to hemorrhage and not to the production or absorption of toxic products.

We made no attempt to ligate all the arteries supplying the portal system, knowing that it would probably be impossible to find them, but more important, because the vessels beyond the ligature would probably be filled anyway through the many anastomotic channels. The presence of significant anastomotic vessels is supported and probably proved by Solowieff [12] who discovered that if the superior mesenteric, gastrosplenic and portal veins were ligated singly, at intervals of five or six days, the animal would not die. These results were verified by Neuhof.[5] Similarly, the slowly stenosing type of thrombosis of the portal vein seen clinically in hepatic cirrhosis fails to produce death, thereby adding support to the assumption that anastomotic vessels will form if the obstruction is not complete and is not produced instantaneously.

12. Solowieff, Alexander: Veränderungen in der Leber unter dem Einflusse künstlicher Verstopfung der Pfortader, Virchows Arch. f. path. Anat. **62**:195, 1875.

6. *Ligation of the Aorta.*—Knowing that ligation of the aorta above the celiac axis would probably prevent entirely the loss of blood into the splanchnic area trapped by the portal ligature, we performed a series of such experiments in dogs as well as cats. As can be seen in table 3, the average duration of life is almost the same in the dogs with ligation of the aorta alone as it is in dogs with simultaneous ligation of the aorta and portal vein, i. e., four hours and thirty-two minutes and four hours and eighteen minutes, respectively. The duration of life of cats with simultaneous ligation of the aorta and portal vein was fifty minutes shorter than the duration of life in cats with ligation of the aorta alone. Tracings of blood pressure taken on several dogs for at least an hour after simultaneous ligation of the aorta and portal vein failed to reveal a semblance of the drop which invariably follows ligation of the portal vein alone (chart 3). If the shock of ligation of the portal vein was due to toxic factors originating in the splanchnic area the animals should die practically as soon after simultaneous ligation of the aorta and portal vein as after ligation of the portal vein alone. That they lived several hours longer is obviously due to the fact that ligation of the aorta prevents the accumulation of blood in the portal system behind the ligature and thus prevents its consequent loss to the general circulation.

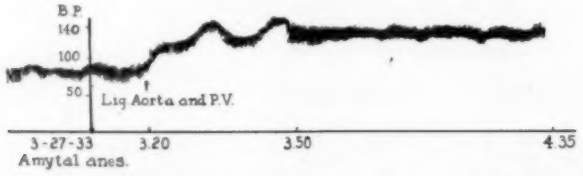

Chart 3.—Blood pressure tracing obtained after the simultaneous ligation of the aorta and the portal vein, showing the absence of a drop which accompanies ligation of the portal vein alone (chart 1). The increased pressure is characteristic of ligation of the aorta.

Lest it be suggested that the presence of blood under pressure in the portal system is a factor in the possible production of a toxin, we conducted some experiments in which, in addition to ligation of the aorta and portal vein, we injected several hundred cubic centimeters of blood into the superior mesenteric artery. This produced the same type of engorgement and cyanosis of the intestines as is seen following portal ligation alone. Thus into the superior mesenteric artery of one dog weighing 6 Kg. we injected 570 cc. of blood, beginning a few minutes after simultaneous ligation of the aorta and portal vein. We repeated the experiment in another dog weighing 6 Kg., injecting 400 cc. of blood into the superior mesenteric artery. The blood pressure was observed for eighty and eighty-five minutes, respectively. There was a sharp rise in the blood pressure at the time the aorta was tied (chart 4), but in neither case did there occur the fall of blood pressure which is characteristic of ligation of the portal vein alone.

Ransohoff [13] demonstrated that simple pressure on the portal vein in animals as well as in human beings produces a sharp and almost immediate fall in blood pressure which, if continued, would probably lead to shock similar to that following actual ligation of the portal vein. This also supports the idea that the effect is due primarily to a loss of blood into the tissues drained by the portal vein.

13. Ransohoff, J. L.: Cause of Sudden Fall in Blood Pressure While Exploring the Common Bile Duct, Ann. Surg. **48**:550, 1908.

He noted the same drop in blood pressure whether the finger was inserted into the foramen of Winslow or a clamp was applied to the portal vein.

7. *Removal of Intestinal Tract.*—After ligation of the portal vein an attempt was made in a few dogs to prolong life by ligation of all vessels and resection of the entire gastro-intestinal tract including the spleen. This can be done in the dog very rapidly. We noted that while this would prevent the usual death, like transfusion of blood, it had to be done before the animal passed into the irremediable stage. On the other hand, even when life was prolonged, the blood pressure remained low and never regained its normal level (chart 5). One of the factors which prevents the blood pressure from regaining its normal level in this experiment may be that the intestinal tract acts as a source of fluid in replenishing the volume of blood after a hemorrhage.

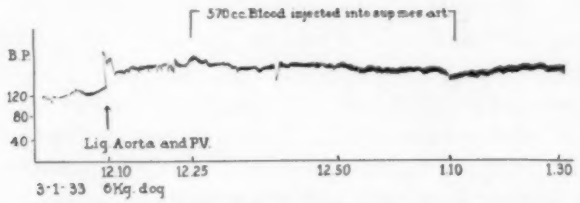

Chart 4.—Blood pressure tracing obtained after simultaneous ligation of the aorta and the portal vein. To imitate the intestinal engorgement characteristic of portal ligation alone, 570 cc. of blood from another dog was injected into the splanchnic area through the superior mesenteric artery. No change in the curve or in the behavior of the animal was observed (compare with chart 3).

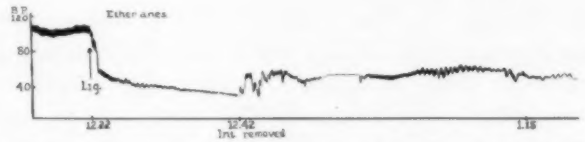

Chart 5.—Blood pressure tracing showing the characteristic fall after ligation (*Lig.*) of the portal vein. Twenty minutes later the entire splanchnic area was resected, with a prompt improvement of blood pressure and prolongation of life, but without regaining the normal level.

COMMENT AND SUMMARY

It seems clear that the rapid death which so regularly follows total and complete occlusion of the portal vein is due to circulatory failure, because of extensive loss of blood from the general circulation into the trapped splanchnic area. No evidence of the production or absorption of a toxic substance (by guinea-pigs and white mice) was found. On the other hand the evidence in favor of the purely physical factor was uniform and consistent, and was obtained from a variety of experiments which, previously described in detail, may be summarized briefly. The increase in weight of the splanchnic area following occlusion of the portal vein was great enough, on the basis of the amount of entrapped

blood it contained, to have caused death from shock alone, since the lost blood was sufficient to lower the systemic blood pressure below that compatible with life. The fall in blood pressure was measured in many animals and was similar to that noted after an extensive hemorrhage except that the pressure was sustained at a low level until death. Moreover, the behavior and appearance of the animal after ligation of the portal vein were similar to those seen after marked loss of blood from hemorrhage. Attempts to raise the blood pressure and prolong life by transfusions of blood were successful, and it was possible to postpone death for over six hours. At this time gangrenous changes in the intestines began to introduce another factor. Finally, it was possible to prolong life and prevent the characteristic fall of blood pressure ordinarily following occlusion of the portal vein by ligating the aorta above the celiac axis, which effectively stopped blood from entering the splanchnic area. These animals lived only a few hours, but they lived as long as animals with ligation of the aorta alone. Moreover, the results of the experiment were the same if in addition several hundred cubic centimeters of blood were injected into the mesenteric arteries to produce the cyanosis and congestion ordinarily seen after ligation of the portal vein.

Death following ligation of the portal vein, while undoubtedly due to the same mechanism as shock from hemorrhage, is probably hastened by the fact that ligation at the same time prevents the gastro-intestinal tract from aiding in the loss of fluid. It is probable that ordinarily much of the fluid which rushes into the circulation to maintain blood volume after a serious hemorrhage comes from the intestinal tract, from which it can most easily be spared. While such a conception rests on a number of clinical observations, its final proof awaits further study.

Another interesting mechanism noted in our experiments was the irremediable changes which occur when a low blood pressure is maintained too long. What this level is probably differs with the individual, but if this critical level is not raised soon enough it can never be corrected, no matter how much blood is transfused. This fact was noted during the World War, when it was found that massive transfusions as well as other means failed to save a soldier who had been in shock for too long a time. The effect may be due to changes produced in the nerve cells. It is likely that too low a pressure slows the metabolic exchange and causes irreparable alteration in the central nervous system. It is known that complete cessation of cerebral circulation for even six minutes may permanently destroy the power of nerve tissue to function even though one can demonstrate no morphologic alteration in the cells. On the other hand, the defect caused by a very low blood pressure may be due to increased capillary permeability. It is obvious that no amount

of blood will succeed in raising the pressure if it leaves the vascular system as fast as it is poured in. The matter merits further experimental study.

CONCLUSIONS

The rapid death which occurs after total and complete ligation of the portal vein is not due to the effect of a toxin elaborated by the gastro-intestinal tract. It is to be explained on the basis of a loss of blood from the systemic into the portal system of a sufficient magnitude to reduce blood pressure below that compatible with life.

FIFTY-THIRD REPORT OF PROGRESS IN ORTHOPEDIC SURGERY

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CONGENITAL AND DEVELOPMENTAL DEFORMITIES

End-Results Following Bloodless Reduction of Congenital Dislocation of the Hip.—Becker [1] reported the end-results in 97 congenital dislocations of the hip in 67 cases from the Erlangen University Clinic, all reduced by von Kryger by the Lorenz method. Following reduction, the hips were kept in plaster casts in the first Lorenz position for six months. This was followed in some instances by rest in bed and by physical therapy. The cases were divided into three groups: (1) those in which reduction was performed over twenty years before the study was made; (2) those in which it was performed ten or more years before, and (3) those in which it was performed over five years before. In the first group there were 36 dislocated hips. Five of these had remained reduced; 4 showed slight subluxation, 12 severe subluxation and 15 redislocation. Of the 4 hips with mild subluxation, 2 showed mild coxa vara and 2 severe coxa vara with marked arthritis deformans, although there was excellent socket formation. Over half of the 12 hips which showed severe subluxation and 13 of the 15 which showed redislocation were painful, the pain usually appearing first in the third

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This Report of Progress is based on a review of 203 articles selected from 337 titles appearing in medical literature approximately between July 1, 1933, and Oct. 28, 1933. Only those which seemed to represent progress have been selected for review.

1. Becker, F.: Deutsche Ztschr. f. Chir. **241**:273, 1933.

decade. All of the reductions with permanent results had been done before the patient was 3½ years of age. There were 19 hips in the second group. Four had remained reduced; 5 showed slight subluxation, 5 severe subluxation and 5 redislocation. The third group consisted of 34 dislocated hips. Five had remained reduced; 15 showed slight subluxation, 7 severe subluxation and 7 redislocation. The femoral head and socket of the hips in which redislocation and severe subluxation occurred were markedly altered. A flat femoral head, anteversion, coxa vara and slipping of the upper femoral epiphysis were observed exactly as in adolescent coxa vara. The femoral head and that half of the pelvis tended to be smaller than on the normal side. In 9 cases there was severe arthritis deformans. It appeared to make no difference so far as function and pain were concerned whether the head made a new socket or hung loosely in the soft tissues. Increasing subluxation or spontaneous healing was apparently uninfluenced by treatment. Early plastic surgical repair of the acetabular roof was suggested as a possible procedure in some of these cases. Only hips in which reduction was proved roentgenologically and clinically offered a good prognosis for the future.

[ED. NOTE.—These end-results are much poorer than those found in many American clinics. Clinical and pathologic studies have taught us that early reduction performed with the minimum of trauma and early, guarded weight-bearing supplemented by physical therapy offer most in these cases.]

Subluxation of the Hip Joint Secondary to Maldevelopment of the Acetabulum.—Simons [2] studied a number of cases of subluxation of the hip joint caused by faulty acetabular development, called by Klapp, "coxa valga luxans." One or both sides of the acetabulum might be affected. In roentgenograms the acetabulum appeared flat and ellipsoid, often without an edge to the acetabular roof. The outer margin of the femoral head was wider than the medial margin, apparently conforming to the shape of the acetabulum. These cases could be differentiated from coxa plana by the character of the upper femoral epiphysis, and were seen chiefly in females. In all of the cases studied arthritis deformans developed later in life.

Congenital Torticollis.—Fitzsimmons [3] discussed the etiology of congenital torticollis. At birth the venous supply of the sternocleidomastoid muscle was obstructed, and fibrosis resulted similar to that seen in the muscles of the forearm in Volkmann's ischemic contracture. The author thought that the ischemia was the result of the temporary venous obstruction, rendered permanent by patchy intravascular clotting.

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2. Simons, B.: Beitr. z. klin. Chir. **157**:505, 1933.
3. Fitzsimmons, H. J.: New England J. Med. **209**:66 (July 13) 1933.

Idiopathic Osteopsathyrosis.—Goin [4] presented a review of the literature on osteopsathyrosis and osteogenesis imperfecta and suggested that the two conditions might be separate diseases or that they might represent different phases of the same disease. The disease occurred in infancy and in childhood and was characterized by a deficiency in the number and function of osteoblasts. There were the hereditary and nonhereditary forms, the former being characterized by blue sclerae. In both, multiple fractures were frequent, which healed rapidly but with deformity. Fractures were rare after puberty, at which time the disease usually subsided. Nothing was known as to the cause or the method of treatment of the disease, but the clinical and roentgenographic findings were characteristic.

TUBERCULOSIS

Tuberculosis in Infancy and in Childhood.—Katzeff [5] made a statistical study of the cases of tuberculosis seen at the Children's Hospital in Boston during a forty-six year period (from 1884 to 1930). The incidence of orthopedic forms of tuberculosis showed a high level during this period and a steady decrease in 1924, with a marked decrease from 1925 to 1930. The lowest point, 22.2 per cent of the total number of cases, was reached in 1930. Just the opposite was true of the nonorthopedic forms of tuberculosis. The incidence rose, until in 1930 a peak of 17.7 per cent was reached. This study confirmed the clinical impression that tuberculosis of the osseous system was a disappearing disease, and that this form of tuberculosis responded more favorably to the measures of preventive medicine than the nonorthopedic forms.

Tuberculosis of the Greater Trochanter.—Meyerding and Mroz [6] reported 19 cases of tuberculosis of the greater trochanter and of the trochanteric bursa. Diagnosis in all the cases was proved. The disease was most prevalent in the first and second decades of life. In 16 of 19 cases, tuberculosis elsewhere in the body (lungs, joints and genitourinary tract) was demonstrated. In only 2 cases was the bursa alone involved. Cure was obtained in both cases by extirpation of the bursa. When the trochanter was involved, radical excision of the infected area was done. Persistent sinuses formed in 4 of the cases. Without treatment, the infection might spread to the neck of the femur and the hip joint.

Tuberculosis of the Diaphysis.—Brower and Downs [7] reported several cases of tuberculous involvement of the diaphysis of the long bones.

4. Goin, L. S.: Am. J. Cancer **17**:668, 1933.

5. Katzeff, M. G.: New England J. Med. **209**:83 (July 13) 1933.

6. Meyerding, H. W., and Mroz, R. J.: Tuberculosis of the Greater Trochanter, J. A. M. A. **101**:1308 (Oct. 21) 1933.

7. Brower, R. S., and Downs, E. E.: Am. J. Roentgenol. **29**:617, 1933.

In 1 case the lesion was confined entirely to the diaphysis of the fibula. An extensive discussion of the etiology was given, including a résumé of the literature. Diagnosis of these lesions was difficult, and as they were rare, the diagnosis was easily missed.

Multiple Tuberculous Spondylitis.—Thrap-Meyer [8] reported the finding of multiple tuberculous spondylitis in 7 patients suffering from pulmonary tuberculosis. In 6 patients there were 2 tuberculous foci in the spine with normal vertebrae between, and in 1 patient there were 3 foci. The author believed that the spinal involvement was of hematogenous origin. He felt that contact with tuberculous abscesses must be considered as a means of spreading the infection to the spine, but he believed this to be rare. In these cases there were no symptoms of irritation of the spinal cord. In all, the symptoms were localized wholly to the caudal focus.

Technic and Dosage of Heliotherapy in Surgical Tuberculosis.—Rollier [9] was of the opinion that heliotherapy to be efficacious should always be strongly individualized. It should be adapted to the season and climate and to the state of the subject's resistance. He enumerated some general rules, however. General heliotherapy should always be carried out, no matter how localized the manifestation of tuberculosis appears to be. Heliotherapy should be given in graduated doses, commencing in all cases with treatment of the extremities; usually three exposures of three minutes each with ten minute rest periods are given. In most cases, after the eighth day exposures can be given with intervals of ten minutes between the periods—for from one to one and one-half hours for the extremities, from three-quarters to one hour for the abdomen, from one-half to three-quarters hour for the thorax and one-quarter hour for the neck. Longer periods of exposure can be given when the skin is well pigmented. Insolation that is interrupted by periods of rest exercises a more tonic and vitalizing action than when it is continuous.

OSTEOMYELITIS

Acute Infectious Osteomyelitis.—From the examination of 262 consecutive cases of acute infectious osteomyelitis, Pyrah and Pain [10] came to the conclusion that moderately conservative treatment was the best for this condition. In the case of average severity they advocated an incision of the periosteum, extending up to the epiphyseal cartilage. Only when frank pus was found by drilling the metaphysis should any opening of the bone be carried out. Compact bone should be removed to uncover the pus, but no further procedure should be used except to

8. Thrap-Meyer, H.: Norsk mag. f. lægevidensk. **94**:641 (June) 1933.
9. Rollier, A.: Brit. J. Phys. Med. **7**:235, 1933.
10. Pyrah, L. N., and Pain, A. B.: Brit. J. Surg. **20**:590, 1933.

provide for drainage and irrigation. If the patient was very ill, or the infection very acute, they felt that treatment should include periosteal incision. In this series of cases there was a mortality of 27.1 per cent.

Osteomyelitis in Ischiopubic Synchondritis.—Haberler [11] reported 3 cases of this condition in children, 2, 6½ and 8 years of age. The disease began with fever, which subsided with rest. The symptoms were those of inflammation of the hip joint, with localized tenderness at the ischiopubic junction. In 1 case a sequestrum formed; in 1 there was complete healing, and in the other there was sclerosis of the bone. Conservative therapy was followed by complete functional recovery. A review of the literature of this rare type of osteomyelitis was given.

FUNGOUS INFECTION OF BONE

Actinomycosis of the Spine.—A case of actinomycosis of the bone was reported by Tabb and Tucker [12] in which the etiology was proved by the recovery of Actinomyces from a draining cervical spine and from the sputum. The spinal lesion was characterized by discrete punched-out areas in the bodies of the tenth and eleventh dorsal vertebrae, without collapse of the vertebral bodies. Large paravertebral masses were seen in the roentgenograms. Pulmonary infection with actinomycosis existed. In spite of the area of the spine involved, there was much less pain than would usually be found with a similar tuberculous lesion.

Blastomycosis of the Bone.—Sixteen cases of blastomycotic infection of the bone were reported by Warding and Blair.[13] The importance of early recognition of the disease by laboratory examination of the exudate was stressed. Osseous lesions, while showing extensive roentgenologic changes, were associated with little fever, with no elevation in the number of white blood cells and with a slowly progressive involvement. In the absence of pulmonary lesions or multiple systemic lesions, cures were observed following therapy with potassium iodide.

[ED. NOTE.—There have been numerous cases of blastomycosis reported, but it is probable that many are overlooked, especially in the early stages of the disease. The 16 cases reported by Tabb and Tucker were found in a thinly populated semirural community.]

POLIOMYELITIS

Acute Poliomyelitis as a Primary Disease of the Central Nervous System.—In a study of acute poliomyelitis, Faber [14] concluded that the clinical course of the disease corresponded with the progress of the infec-

11. Haberler, G.: Arch. f. klin. Chir. **175**:625, 1933.
12. Tabb, J. L., and Tucker, J. T.: Am. J. Roentgenol. **29**:628, 1933.
13. Warding, D. B., and Blair, C. C.: South. M. J. **26**:315, 1933.
14. Faber, H. K.: Medicine **12**:83, 1933.

tion through and within the central nervous system, the portal of entry being the olfactory mucosa. The virus spread by extension from the olfactory bulb through the olfactory tracts to the interbrain (the hypothalamus and thalamus), thence through the spinothalamic tract to the posterior horns and intervertebral ganglions of the cord, where it produced the later preparalytic symptoms, and thence to the anterior spinal horns. In discussing the therapy, the author felt that serum, and especially tested human serum, should be administered intravenously in large doses. Considering the early infiltration of the involved areas of the cord, the author believed that by intrathecal injection of serum the immune antibodies reached the infected areas in insufficient concentration. It was by the intravenous injection of large amounts of tested serum that results might be obtained. With the present knowledge of the disease, the author did not feel justified in discarding the use of serum of known antibody potency.

[ED. NOTE.—This article of more than 100 pages cannot be discussed adequately in a brief abstract. It merits careful reading for those interested in acute poliomyelitis. The final word has not yet been said in regard to serums in the early treatment of poliomyelitis.]

Treatment of Acute Poliomyelitis with Transfusions of Convalescent Blood.—Sherman [15] treated 71 patients suffering from poliomyelitis with transfusions of whole blood from donors convalescing from poliomyelitis. From 150 to 400 cc. of blood was given intravenously. Thirty-five patients were in the preparalytic stage, while 36 were paralyzed. There were 5 deaths; 2 of the patients were moribund when the transfusion was given. Paralysis developed in only 3 of those treated in the preparalytic stage. In some of the cases transfusion seemed to be beneficial in shortening the period of fever and the duration of other symptoms of the disease. The author advocated the registration of persons who had recovered from poliomyelitis for use as donors in epidemics.

CHRONIC ARTHRITIS

Rheumatic Conditions of the Tendon and Muscle Attachments.—Under the term "tendinitis," Kahlmeter [16] described a condition of tenderness, swelling and pain of the muscle or of its tendinous attachments, not implying thereby that true inflammatory changes were present. The general form, "polytendinitis," was shown to resemble acute rheumatic polyarthritis closely, and the local form to include such conditions as tennis elbow and calcaneal spur. Especial attention was drawn to tenderness of the quadriceps tendon at the upper border of the

15. Sherman, T.: Deutsche med. Wchnschr. **59**:1332, 1933.
16. Kahlmeter, G.: Lancet **1**:1338 (June 24) 1933.

patella. The author had 25 patients with this condition. They experienced pain on walking which radiated up the front of the thigh, but there was no swelling of the knee joint or any tenderness except in the localized area above the patella. Cure was obtained in all cases of "tendinitis" by roentgen treatment. Unfortunately, no indication was given as to the appropiate dosage.

Economics of Rheumatism.—From the government report of 1924, Buckley [17] deduced that "rheumatism" accounted for one sixth of the industrial invalidism in England and concluded that the loss of wages and disbursements by approved societies for sickness, etc., amounted to more than 20,000,000 pounds for the year. He was of the opinion that the problem was so extensive that voluntary hospitals could not cope with it, and cited the methods of financing more elaborate schemes which were in operation in many countries and included, when necessary, reeducation for new employment.

Transitory Arthritis of the Hip Joint in Childhood.—The necessity for early and exact diagnosis of arthritis of the hip in children was emphasized by Butler,[18] who gave a report of an investigation in 97 cases. Of these, 56 were proved to be tuberculous and 34 to be of a transitory nature, with no abnormality shown by roentgenographic examination. Seven occurred as reactions to localized infection of the bones near the joints. All persons with questionable arthritis of the hips were admitted to the hospital to be observed, and were treated by rest, extension or fixation according to their individual requirements. The transitory type of arthritis cleared up excellently, and its chief importance lay in the fact that clinically it so closely resembled an early tuberculous infection. In the vast majority of the cases an entirely negative roentgen picture could be taken to exclude a tuberculous infection.

SCOLIOSIS

Mechanics of Scoliosis.—Rogers [19] reviewed the various theories of the mechanics of scoliosis and showed that none of them was adequate to explain the entire mechanical evolution of scoliosis. He grouped the muscles acting on the spinal column into flexor, extensor, deep torsion and transverse traction muscles. It was found that a unilateral relaxation of the extensor group of muscles could produce the three elements of deformity in scoliosis; lateral deviation, rotation and kyphosis. The author believed that hyperextension was the best mechanical position in which to treat scoliotic deformities.

17. Buckley, C. W.: J. State Med. **41**:282, 1933.
18. Butler, R. W.: Brit. M. J. **1**:951 (June 3) 1933.
19. Rogers, S. P.: Mechanics of Scoliosis, Arch. Surg. **26**:962 (June) 1933.

THE SPINE

Changes in the Articulations of the Vertebral Processes, a Little Considered Cause of Backache.—Lange [20] called attention to changes in the articulations of the vertebral processes as found in various disabilities. Special technic was necessary to demonstrate these changes in the roentgenograms; for the cervical vertebrae, the articulations were best shown in lateral views with the neck in full extension; for the dorsal spine, the roentgenograms were taken from the side with the patient turned from 15 to 20 degrees from the true lateral position with the scapula rotated outward; for the lumbar spine, the articulations were shown in anteroposterior views and in views taken at a deviation of 45 degrees from the true lateral position. The changes commonly found in conditions such as scoliosis, vertebral fractures and postural changes in stout persons were first a loss of the parallel form of the surface of the joints followed by arthritic changes. The author discussed the possible relationship of these changes to pain and to limitation of motion in the spine.

Backache from Relaxation of the Sacro-Iliac Joint.—Bragard,[21] in Lange's Clinic in Munich, reviewed over 100 cases of backache caused by relaxation of the sacro-iliac joint. He attempted to explain on an anatomic background the symptomatology and the reactions to the various diagnostic tests. Pain, he believed, was due to a tearing of the articular capsule and to overstretching of the surrounding ligaments and muscles; later there appeared degeneration of the articular cartilage, periostitis and arthritic changes. Roentgenograms helped very little in diagnosis. Treatment in the acute cases consisted of circular adhesive strapping from the trochanters to the navel. This strapping was renewed if pain was still acute. A pelvic band or corset was next used. Heat or diathermy and massage were given, and later gymnastics were advocated, first with passive, and later with active, motion. Operations for the relief of symptoms, such as are described in the American literature, were not required in any of these cases.

TUMORS

Bone Endothelioma and Primary Epithelial Bone Tumors.—Petrow and Glasunow [22] collected 7 cases of primary epithelial tumor of the long bones from the literature and added a case of their own. They concluded that a number of the endotheliomas of the bone reported in the past were metastatic epithelial tumors; others were probably caused by metastases, and still others were of unknown origin. Epithelial

20. Lange, M.: München. med. Wchnschr. **80**:1134 (July 21) 1933.
21. Bragard, K.: München. med. Wchnschr. **80**:1240 (Aug. 11) 1933.
22. Petrow, N., and Glasunow, M.: Arch. f. klin. Chir. **175**:589, 1933.

tumors must be included in primary tumors of the bone. Their origin was probably in embryonic ectodermal inclusions. These tumors almost always involved the tibia. Histologically, they were similar to basal cell carcinoma. It was not definitely known whether or not they were malignant.

Primary Echinococcosis of Vertebra.—Pessano [23] reported 2 cases of hydatid cyst of the vertebra, one in a 26 year old man with a lesion between the eighth and the twelfth dorsal vertebra and the other in a 14 year old girl. The diagnosis was made only after exploratory operation, the usual diagnosis before operation being tuberculous spondylitis. Compression of the spinal column was common. Often no symptoms were present until trauma to the spine occurred. Surgical intervention with evacuation and destruction of the cysts was the treatment of choice. Arsenical preparations were an aid in treatment. The cysts were always multilocular and were found in the spongy or areolar tissue of the vertebral body. A complete review of the literature was given.

CIRCULATORY DISTURBANCES OF THE EXTREMITIES

Study of the Dorsalis Pedis and Posterior Tibial Pulses in One Thousand Persons Without Symptoms of Circulatory Conditions of the Extremities.—Morrison [24] studied the pulse in the posterior tibial and dorsalis pedis arteries in 1,000 persons who had no symptoms of any circulatory disturbance in the extremities. Absence of the pulse in one or more of the vessels was noted in 191 persons. All pulsations were absent in 19. Absence of pulsation was more common in the posterior tibial than in the dorsalis pedis arteries. The patients with absent pulsation were of all ages. The author stated that absence of pulsation did not necessarily mean disease of the arteries.

Evaluation of Various Methods of Investigating the Circulation in the Lower Extremities.—Kramer [25] attempted to evaluate the various methods of investigation of the circulation in the lower extremities by considering the oscillometer, injections of histamine, heat, measurements, intradermal injections of salt solution, roentgenograms, roentgenographic visualization of the vessels and the sphygmotonograph. In many instances the author found that a careful history and physical examination did not give adequate data in regard to the circulation. The conclusions drawn were that all of these methods had merit. The oscillometer gave evidence of circulation in deep vessels which could not be palpated. Injections of histamine were of value, particularly for the study of the superficial circulation. Roentgen studies were of little

23. Pessano, J. E.: Semana méd. **1**:2126 (June 29) 1933.
24. Morrison, H.: New England J. Med. **208**:438 (Feb. 23) 1933.
25. Kramer, D. W.: Am. J. M. Sc. **185**:402, 1933.

value, except in rare instances, particularly in cases of diabetes. The calorimetric methods were chiefly of value in differentiating between vasospastic and occlusive lesions of the vessels.

RUPTURES OF MUSCLES AND TENDONS

Spontaneous Rupture of the Long Tendon of the Biceps.—Oppolzer [26] was able to collect over 200 cases of rupture of the long tendon of the biceps brachialis muscle. It was found most commonly in muscular persons and particularly on the left side in glass blowers. In less muscular men, it was seen only after the age of 45. In the author's own cases the classic signs were absent. These were known as Heuter's sign (pain in the shoulder when the supinated forearm was flexed), Pagenstecher's sign (subluxation of the humeral head upward and inward) and Cruveilhier's sign (elevation of the humeral head). Conservative treatment was advised for persons too old to perform heavy work. The author sutured the peripheral portion of the tendon beneath the tendon of the pectoralis major muscle to the pectoralis attachment on the humerus. Various authors had estimated the disability from this injury to be from 10 to 50 per cent.

Separation of the Symphysis Pubis.—Boland [27] reported 10 cases of separation of the symphysis pubis occurring during delivery. He found the ratio to be 1 in 685 deliveries. He believed that this lesion was due to trauma resulting from the descent of the fetal head associated with an inherent weakness of the ligaments about the symphysis. Associated with the separation of the symphysis pubis was involvement of the sacro-iliac joints and posterior displacement of the acetabula. The onset of the symptoms was usually acute with pain over the symphysis and in the lower part of the back. The onset of symptoms varied from two months before delivery to twelve days after delivery. On physical examination there was often a separation of the symphysis pubis of from one to two fingerbreadths; a waddling gait was frequently observed, and tenderness was present over the sacro-iliac joints. Treatment consisted in placing the patient on a hard bed and in circular strapping of the pelvis with adhesive plaster. If one pubis was elevated in the roentgenograms, traction was applied to the leg on that side until the pubes were level. When there was wide separation, a canvas hammock with overhead traction on the sides was used. For later convalescence, a butterfly type of brace was applied. This separation appearing in pregnancy was no indication for immediate delivery. It was treated as a complication, and delivery was allowed to proceed to term. The separation was found to recur in each succeeding pregnancy.

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26. Oppolzer, R.: Deutsche Ztschr. f. Chir. **241**:281, 1933.
27. Boland, B. F.: New England J. Med. **208**:431 (Feb. 23) 1933.

MISCELLANEOUS

Injuries of the Semilunar Cartilage.—Wright [28] reported on the conservative treatment of a group of patients with primary or recurrent dislocation of the internal semilunar cartilage. They were treated by the following definite routine: 1. The displaced cartilage was reduced by manipulation, preferably with the patient under the influence of an anesthetic. 2. From 5 to 10 minims (0.3 to 0.6 cc.) of tincture of iodine was injected at the point of greatest tenderness. The author felt that this stimulated the feeble reparative process of the cartilage. 3. Fixation of the leg in full extension in a light plaster cast was carried out. 4. Walking was encouraged in the cast after two days. 5. Faradic stimulation was used to aid in the redevelopment of the weakened quadriceps muscle. 6. The inner border of the heel was raised to remove the strain from the knee. Five primary and 28 recurrent dislocations were treated in this manner. One patient failed to improve, and the cartilage was removed by operation. Two patients failed to report for follow-up examination. The rest showed excellent results. There were no recurrences of the dislocation.

Adaptation to New Function by Muscles Shifted in the Course of Tendon Transplantation.—Lange,[29] after many years of experience in the transplantation of tendons, concluded that muscles shifted in their course adapted themselves to new functions only after long and careful training. His procedure had been to leave the limb in a plaster cast for six weeks. Occasionally, electrical stimulation of the transplanted muscle was begun in the fifth week. After the cast was taken off, the limb was placed in a apparatus which moved the affected joint by millimeter gradations. By such methods the intelligent patient learned to use the transplanted muscle in from a few weeks to several months. The author reported the use of silk tendons for various types of muscle transplantation.

The Possibility of Recording Noises Produced in Joints.—Erb,[30] by the use of an oscillograph, was able to record the noises produced in knee joints and to analyze to some degree their frequency and significance. Not only were the noises recorded that are usually heard but also others the character of which had not yet been studied.

Bony Nucleus of the Anterior Inferior Iliac Spine.—Janker [31] observed 2 cases in which the anterior inferior iliac spine had not fused on one side at the age of 18 and on both sides at the age of 20. Anatomists have taught that the nucleus of this process appears at the age

28. Wright, C. S.: Canad. M. A. J. **28**:618 (June) 1933.
29. Lange, F.: München. med. Wchnschr. **80**:1133 (July 21) 1933.
30. Erb, K. H.: Deutsche Ztschr. f. Chir. **241**:236, 1933.
31. Janker, R.: Deutsche Ztschr. f. Chir. **241**:477, 1933.

of 15 or 16 and fuses within a year. Such osseous nuclei not fused to the ileum might be confused with avulsions when injury has occurred in this region.

ORTHOPEDIC OPERATIONS

Treatment of Athetosis and Dystonia by Section of the Extrapyramidal Motor Tracts.—Putnam [32] sectioned the extrapyramidal motor tracts in 5 cases of athetosis and dystonia. In 4 of the cases there was definite improvement as far as the uncontrolled muscular activity was concerned. There were no permanent ill effects from the operation. The operation in each case was described, and the histories were presented.

Treatment of Injuries of the Semilunar Cartilage.—Stefanini [33] reviewed the various incisions used in operating on semilunar cartilage. He objected to most of them because they did not allow sufficient exposure for the total removal of the cartilage. Failure to remove the posterior part of an injured cartilage sometimes resulted in recurrence of symptoms, necessitating a second operation. The author preferred an enlargement of Baker's incision, making a J with the long arm parallel to the patella and then turning the incision outward as far as the lateral ligament.

[Ed. Note.—Just how this incision gives better exposure to the posterior portion of the cartilage than the incision of Timbrel Fisher is difficult to see. The noteworthy point, however, seems to us to be that it is important to remove the whole cartilage and to use an incision that allows access to the posterior rim of the cartilage.]

Countersinking the Astragalus.—Brewster [34] described an operation which he has performed for the last six years on paralyzed feet. This consisted of countersinking the previously prepared astragalus into a rectangular well in the os calcis. This procedure enabled the operator to set the foot well back, to lower the tibioastragalar joint so that dorsal and plantar flexion were limited, and to gain lateral stability by fusion of the calcaneo-astragaloid joint.

[Ed. Note.—This operation seems to offer the advantages of an astragalectomy without the operative difficulty and without the resulting mutilation.]

Tendon Transplantation in the Lower Extremity.—Ober [35] discussed the general considerations of tendon transplantation. In the cases selected for operation, he said, all the tendons must have sufficient power

32. Putnam, T. J.: Treatment of Athetosis and Dystonia by Section of Extrapyramidal Motor Tracts, Arch. Neurol. & Psychiat. **29**:504 (March) 1933.

33. Stefanini, J.: Rev. de chir., Paris **52**:349, 1933.

34. Brewster, A. H.: New England J. Med. **209**:71 (July 13) 1933.

35. Ober, F. R.: New England J. Med. **209**:52 (July 13) 1933.

so that when one is transplanted the others will continue to stabilize the joint. Deformities must be corrected (as by stabilizing operations) before transplantation is done. The tendon selected for transplantation should have power enough to balance its opponent. Adhesions must be prevented, and the question of leverage must be considered. The tendon should be inserted preferably into bone. The transplanted tendon should parallel as nearly as possible the course of the paralyzed one. As a general rule, the transplant should be under enough tension to hold the foot in a corrected position. Various tendon transplantations about the ankle, knee and hip joints were discussed in detail and the operative technic was described.

Resection of the Shoulder Joint in Tuberculosis.—Richard and Courvoisier [36] stated that surgical treatment of the upper extremity was the opposite of treatment of the lower extremity. In the lower extremity fusion was desired, but in the upper extremity, motion. They considered that fusion of the shoulder joint was being done too frequently, and that resection was preferable when possible. Conditions essential to resection were: (1) good musculature about the shoulder, with recognition of the fact that some atrophy is invariably present, and (2) intact nerves. Contraindications were: (1) very active lesions with multiple open sinuses, resection in these cases resulting in ankylosis, and (2) old quiescent lesions that had caused ankylosis and resulted in extreme muscular atrophy. Except for these contraindications, the joint of the shoulder was always amenable to resection. The presence of an abscess or a sinus was not a contraindication. Through an anterior incision the muscular attachments at the tuberosities were separated; subsequently the humeral head was removed at the surgical neck except in children in whom the epiphysis was left intact. The articular cartilage was then curetted from the glenoid. Particular care was taken to preserve the deltoid muscle and its nerve supply. From two to five weeks of mobilization followed. Cases illustrating both good and bad results were described.

FRACTURES AND DISLOCATIONS

Avulsions of the Carpal Bones.—Ernst and Römmelt [37] called attention to avulsions of small portions of the periosteum and bone from the carpal bones. Ninety personal observations were recorded. In his own material of 6,000 wrists the roentgenograms showed no definite accessory bones. Lesions of the semilunar and large multiangular bones were most commonly found to cause pain. The other bones healed in

36. Richard, A., and Courvoisier, J. N.: Presse méd. **41**:290 (Feb. 22) 1933.
37. Ernst, M., and Römmelt, W.: Deutsche Ztschr. f. Chir. **241**:438, 1933.

a few days. Traces of such injury could be demonstrated in the roentgenograms for long periods.

Mechanics of Supracondylar Fracture of the Humerus.—Coenen [38] divided supracondylar fractures according to the mechanism causing the fracture into flexion and extension fractures. In a group of 38 supracondylar fractures, 29 were flexion fractures and 9 extension fractures. The flexion type of fracture was caused by a fall on the forearm portion of the acutely flexed elbow. The fracture line was higher on the posterior aspect of the humerus than on the anterior aspect. The extension type of fracture resulted from a fall or blow on the upper arm portion of the elbow. This caused the fracture line to be higher on the anterior aspect of the humerus than on the posterior aspect. Reduction of the flexion type was secured by traction on the forearm forward and distally, with acute flexion of the elbow. Reduction of the extension type of fracture was more difficult, and skeletal traction through the olecranon was sometimes required.

Fractures and Dislocations in the Region of the Elbow.—Wilson [39] made a study of 176 cases of injury about the elbow all of which had been followed for at least a year. Each type of injury was discussed from the point of view of treatment and prognosis, and attention was called to the various complications and dangers that should be avoided. Conclusions drawn from the whole groups were that proper treatment which commenced early obtained better end-results than are commonly supposed to occur in such injuries.

[Ed. Note.—This paper is a detailed exposition on the treatment of injuries about the elbow. It represents part of a seven years' study of 4,536 bony injuries treated in the service for fractures of the Massachusetts General Hospital.]

Ununited Fractures of the Shaft of the Humerus.—Owen [40] considered ununited fractures of the humeral shaft to be those in which there was no evidence of union six months after injury. At the time stimulation of union was difficult, and half-way measures were unavailing. He advised an autogenous bone graft followed by fixation for four months. Foreign materials were avoided, as it was considered that in spite of firm fixation they often hindered union. In 7 of the 8 cases reported the results were successful.

[Ed. Note.—The experience of the editors is in entire accord with these findings.]

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38. Coenen, H.: München. med. Wchnschr. **80**:1174 (July 28) 1933.

39. Wilson, P. D.: Surg., Gynec. & Obst. **56**:335, 1933

40. Owen, W. B.: Ununited Fractures of the Shaft of the Humerus, J. A. M. A. **101**:569 (Aug. 19) 1933.

Recognition of Fractures of the Laminae of Vertebrae in the Roentgenogram.—Von Oettingen [41] called attention to the difficulty of recognizing fractures of the laminae of vertebrae, particularly late after injury. He urged careful examination of early roentgenograms with this lesion in mind. Fractures extending through the pedicles into the transverse processes might be difficult to recognize after healing has occurred, save for the residual broadening of the transverse processes.

Intra-Articular Fractures of the Proximal End of the Tibia.—Mikkelsen [42] reviewed 248 cases of intra-articular fractures of the proximal end of the tibia—160 from the Kommune Hospital in Copenhagen and 88 industrial cases. The end-results were recorded in 126 of the 160 cases from one to nineteen years after the injury. Examination was done in 56 of the 88 industrial cases at the end of a year, and in the remainder, from two to five years after the fracture. The cases were classified as follows: (1) 51 medial and 116 lateral unicondylar fractures; (2) 25 bicondylar Y and V fractures, 16 T fractures and 5 comminuted fractures; (3) 18 fractures of the tibial spine and (4) 9 unusual fractures. The mechanism causing the injury was discussed for each group. In most instances it was a horizontal force acting directly on the condyles. Almost all of the patients were middle-aged. Two were 12 years of age. Treatment in most of the cases consisted of a pillow type of splint which permitted early motion and massage of the knee. Puncture of the joint was done for hemarthrosis. Operation was resorted to in only a few cases of unicondylar fracture with marked dislocation. Direct extension was avoided on account of stretching of articular ligaments. The patients were kept in bed for eight weeks, and longer if there was lateral instability of the knee. Fifty-four per cent of the 160 patients in the hospital showed complete recovery functionally, and 90 per cent were doing their usual work. The industrial cases were influenced by the question of indemnity. Complete recovery was found in only 5 per cent of the patients in this group, and only 29 per cent were doing their usual work.

Immediate Treatment of Compound Fractures.—Orr [43] stressed the advantages of immediate direct fixation of the fragments in compound fractures. The disadvantages and dangers, he believed, were lessened by complete immobilization with dressing by the Orr method. He presented a case illustrating how this method might lead to primary union and reduce the length of the period of disability.

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41. von Oettingen, E. N.: Deutsche Ztschr. f. Chir. **241**:471, 1933.

42. Mikkelsen, O.: Acta chir. Scandinav. **73**:1, 1933.

43. Orr, H. W.: The Immediate Treatment of Compound Fractures: The Albee Bone Graft and the Winnett Orr Method of Postoperative Care, J. A. M. A. **101**:1378 (Oct. 28) 1933.

[ED. NOTE.—Primary fixation of compound fractures is desirable, and if the danger of its application can be lessened by this or other methods a considerable advance in the treatment of fractures will have been attained.]

Clinical Study of the Cause of Pseudarthrosis of the Diaphysis of the Long Bones.—Hellstadius [44] made a careful study of 70 cases of pseudarthrosis of the long bones of the extremities. Most of the patients were in Haglund's clinic in Stockholm. The author felt that probably all cases of pseudarthrosis began as a delayed consolidation; in 34 cases there was much callus, and in only 12, no callus. He observed that as pseudarthrosis developed, the periosteal callus smoothed out. Pseudarthrosis developed rarely in children; there were no cases in children under 10. No disease process except syphilis seemed to delay union. In this series only 1 patient, a diabetic subject, was not robust. Glands of internal secretion and vitamins seemed to play a minor rôle in pseudarthrosis, as seen in these cases. Fracture of two bones did not particularly influence the tendency to nonunion. There were 10 cases of pseudarthrosis of the forearm; 5 of both bones, 3 of the radius and 2 of the ulna. There were 29 cases of pseudarthrosis of the bones of the lower part of the leg; 25 of the tibia and 4 of the tibia and fibula. The author concluded that some local predisposition or inhibiting factor led to the pseudarthrosis. This condition was most commonly observed in comminuted fractures where the circulation was poorest. No definite statement could be made as to injury of the nutritive artery, but in 23 of the 70 cases the midpart of the diaphysis was involved. Pseudarthrosis was more common after transverse than after spiral or oblique fractures. In this series there were 31 comminuted, 23 transverse, and 4 oblique fractures. Seven per cent of the cases occurred after compound fractures. In a large series of fractures, pseudarthrosis was found in 2.4 per cent of those operated on and in 0.23 per cent of those reduced manually. In the author's opinion, interposition of the soft parts did not cause nonunion. Nonunion was more common after horn or bone grafts than after the use of Lane plates. Early operation predisposed to nonunion. The best time to perform operation on fractures was during the second week. Violence with laceration and tearing of the soft parts seemed to be the chief predisposing cause. Separation of fragments contributed to nonunion only in that the masses of callus from the ends of the fracture had a longer distance to bridge. Faulty immobilization was of importance as a factor in nonunion only in the later stages when the masses of callus coalesced.

44. Hellstadius, A.: Acta chir. Scandinav. **73**:111, 1933.

PATHOLOGY OF BONE AND JOINT LESIONS

Normal and Pathologic Histology of the Meniscus of the Knee.—In a concise paper, Tobler [45] discussed his conclusions on a study of 1,000 menisci from cadavers and of 400 operatively removed specimens. His findings were based on personal observations. Degenerative changes occurred regularly in normal cartilage after the age of 15. After the age of 32, all cartilage showed fatty degeneration. Also, degeneration of bundles of connective tissue fibers was seen regularly after the age of 37. These changes led to clefts. Ganglions, calcification, ossification and acute inflammatory changes in sepsis were reported and illustrated. Degenerative changes make the meniscus ready for injury. The author stated: "Every meniscus which became torn was already degenerated. The degenerative changes were not the result of injury as hitherto presupposed, but the cause of it." Reparative changes occurred in the portion of cartilage not torn free. In operations, therefore, Tobler never removed the whole cartilage except in cysts of the external meniscus) but left the portion attached to the capsule intact to regenerate new cartilage. He had observed such cartilages a number of times at reoperation.

[ED. NOTE.—The occurrence of these degenerative changes since the work of Mandl (not credited by Tobler) are gaining ever-increasing recognition among those interested in articular pathology.]

Histologic Changes in the Bone Responsible for the Action of Parathyroid Hormone on Calcium Metabolism in Rats.—In an investigation of the histologic changes in the bones of rats fed on parathyroid hormone, Pugsley and Seyle [46] showed that during the period when serum calcium was increased, i. e., four days, there was marked proliferation of the osteoclasts. This was taken to be analogous to osteitis fibrosa. Thereafter, as the level of the serum calcium returned to normal, osteoblastic proliferation was seen, and it was suggested that if the administration of the hormone was continued, "marble bone" would result.

Resected Knee Joints.—Ghormley and Brav [47] reviewed the clinical history, roentgenographic findings, gross and microscopic pathologic changes and the results of inoculation of guinea-pigs in 236 resections and 9 amputations of the knee joint. They found that the preoperative diagnosis was correct in 24.4 per cent of the cases of tuberculosis. The diagnosis based on microscopic examination of tissue was accurate in all but 3.2 per cent of the cases.

45. Tobler, T.: Arch. f. klin. Chir. **177**:482, 1933

46. Pugsley, L. I., and Seyle, H.: J. Physiol. **79**:31, 1933.

47. Ghormley, R. K., and Brav, E. A.: Resected Knee Joint, Arch. Surg. **26**: 465 (March) 1933.

RESEARCH

Effect of Roentgen Rays on Bone Growth and Bone Regeneration.—Brooks and Hillstrom [48] studied the effect of the roentgen rays on the growth and regeneration of bone in rabbits. A single 100 per cent skin erythema dose was given to one tibia, and the animal was killed in from one to twenty-six days. Marked inhibition of growth was noticed, which was limited to the exposed bone. Smaller doses of the roentgen rays, 40 per cent or more of a skin erythema dose, retarded growth proportionately to the amount given. Very small repeated doses, from 2 to 5 per cent, caused no stimulation or inhibition; 150 per cent of a skin erythema dose repeated on the following day caused about the same amount of retardation as a 100 per cent skin erythema dose. A skin erythema dose of 160 per cent given four times produced less retardation of growth than 1 skin erythema dose of 100 per cent. Microscopic study of the exposed bones showed serious damage and at times complete absence of proliferating cartilage. Repair of bone defects was not inhibited; growth alone was disturbed.

Influence of Periosteum on the Survival of Bone Grafts.—Haldeman [49] carried out experiments on young rabbits in which he transplanted bone from the tibia and the fibula to operative defects in the radius. He noted the rate of healing of the fracture after the transplantation of (1) fibula with periosteum, (2) grafts of periosteum alone, (3) osteoperiosteal grafts and (4) grafts consisting of cortex and of periosteum. It was found that grafts with periosteum favored the early closure of the defect and the survival of the graft. It was concluded that the periosteum was the most important part of the graft.

Growth of Epiphyses of the Long Bones in Madder-Fed Pigs.—From the measurements of the epiphyses of a dozen madder-fed pigs over a period of five hundred and seven days, Payton [50] concluded that growth in the length of the epiphyses took place on the side near the joint, and he found that absorption occurred on the diaphyseal side. The investigation supported Stevenson's statement that there was an age sequence of union of the epiphyses, and Humphry's statement that "the end of the shaft at which the epiphysis is last united is the end at which growth takes place most quickly."

Experimental Bone Tuberculosis.—According to Mandelstamm,[51] the localization of tuberculosis in the long bones was not the result primarily of vascular distribution, but the expression of a local immunity which varies with tissues. The epiphyses showed a greater tendency

48. Brooks, B., and Hillstrom, H. T.: Am. J. Surg. **20**:599 (June) 1933.
49. Haldeman, K. O.: J. Bone & Joint Surg. **15**:302, 1933.
50. Payton, G. C.: J. Anat. **67**:371, 1933.
51. Mandelstamm, M.: Beitr. z. Klin. d. Tuberk. **82**:98, 1933.

to develop tuberculosis than the diaphyseal marrow. In the latter, when tubercles formed in the myeloid tissue, the tendency to regression was marked. Yet when the animal had been previously subjected to a severe attack of fever by injections of typhoid germs the diaphyseal tuberculosis which was produced progressed rapidly. The tubercle did not develop in fatty marrow.

Aseptic Necrosis of the Head of the Femur Following Traumatic Dislocation of the Hip Joint.—Stewart [52] produced aseptic necrosis in young and in adult rabbits by (1) dividing the ligamentum teres femoris and by (2) dividing the ligamentum teres femoris and cutting, in a circular manner, the periosteum of the femoral neck below the head. Division of the ligamentum teres femoris and cutting of the periosteum were only partially successful in producing aseptic necrosis. The ligaments showed a great tendency to reunite, and no marked change occurred when the ligament alone was cut. It was also necessary to interrupt the blood supply of the femoral neck to produce real necrosis of the head.

Manner of Removal of Protein from Normal Joints.—Bauer and his co-workers [53] showed that albumin fractions of protein injected into the normal joints of dogs were readily removed by way of the lymphatic system, and that exercise and massage of the limb hastened this removal. Globulin was removed slowly if at all. The blood stream was an unimportant factor in the removal of protein from a joint.

[ED. NOTE.—These experiments cast new light on the well known fact that massage of the muscles about a joint hastens the removal of a synovial effusion.]

(To be concluded)

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52. Stewart, W. J.: J. Bone & Joint Surg. **15**:413 (July) 1933.

53. Bauer, W.; Bennett, G. A., and Short, J. A.: J. Exper. Med. **57**:419, 1933.

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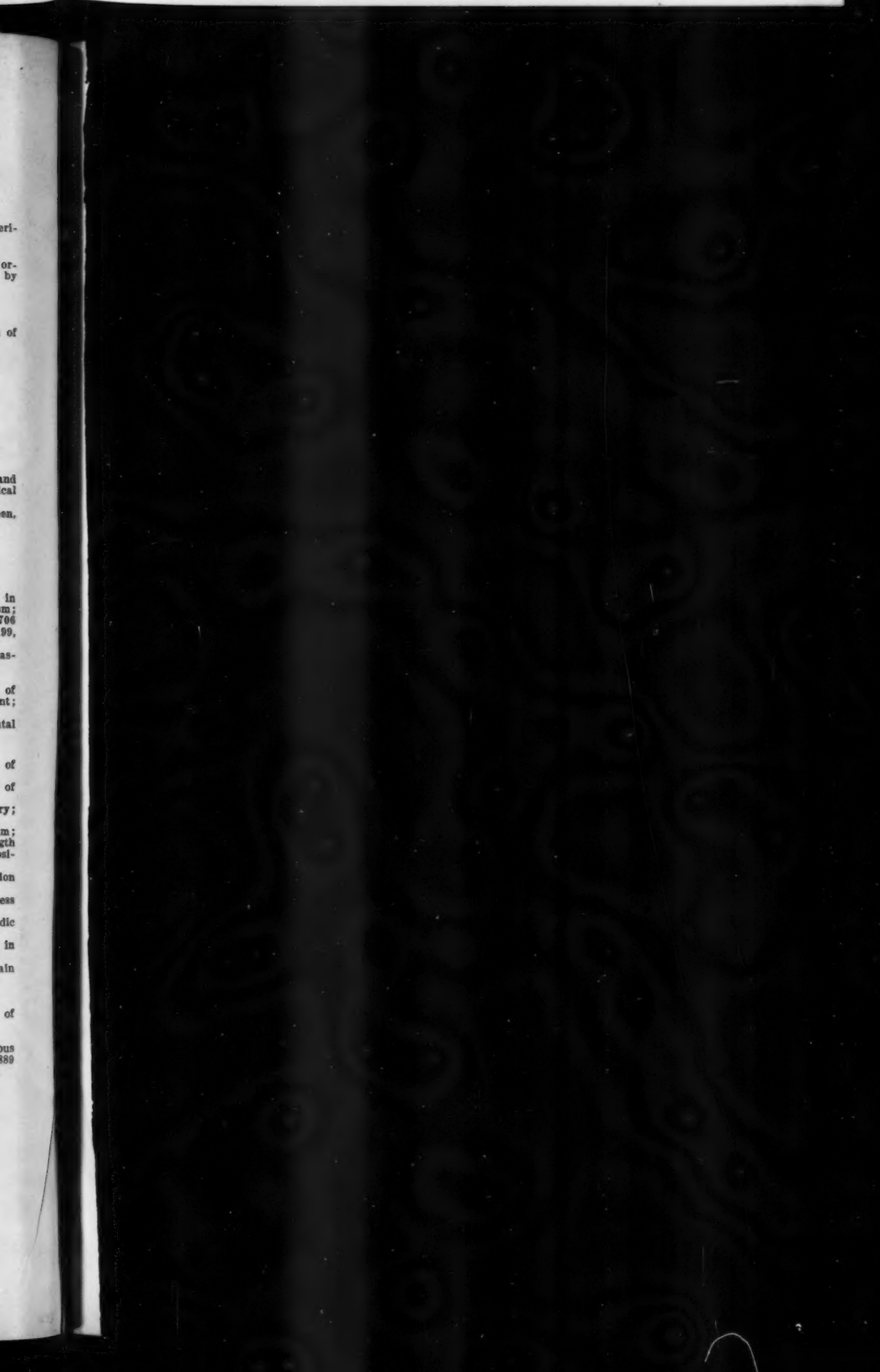
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